Ocular cicatricial pemphigoid treated with intramuscular corticotropin injections

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INTRODUCTION

Mucous membrane pemphigoid is a rare, chronic, autoimmune blistering disorder affecting mucosal surfaces. Ocular cicatricial pemphigoid is a subgroup of mucous membrane pemphigoid with nearly exclusive ocular involvement. Ocular involvement is commonly bilateral and can lead to complications such as scar formation, trichiasis, entropion, corneal ulceration, and blindness. There are multiple options to treat patients with moderate to severe ocular cicatricial pemphigoid, including steroid-sparing medications, but each one has its own adverse effect profile that may preclude usage. Adrenocorticotropic hormone, or corticotropin, is a melanocortin derived from the precursor molecule proopiomelanocortin that is endogenously produced as part of the hypothalamic-pituitary pathway to stimulate endogenous steroid production. We present an 80-year-old woman with long-standing history of ocular cicatricial pemphigoid who failed multiple steroid-sparing immunosuppressive medications and whose disease was successfully controlled with intramuscular corticotropin injections as monotherapy.

CASE REPORT

An 80-year-old woman with long-standing history of ocular cicatricial pemphigoid presented to the clinic for management of her disease. She had previously had a mucosal biopsy of bilateral conjunctiva with a direct immunofluorescence test result showing IgG and IgA in the subepithelial mucosa and a discontinuous linear to granular C3 deposition at the epithelial-mucosa junction, consistent with ocular cicatricial pemphigoid. She had previously failed dapsone 100 mg (she developed anemia), mycophenolic acid 720 mg twice a day (she developed ischemic colitis), and oral methotrexate 20 mg weekly. She also had been treated with a prednisone taper starting at 40 mg daily, which was decreased by 10 mg every 2 days until a stable dose of 10 mg, but subjectively had decreased energy, and this was discontinued. Her disease had stabilized while she received azathioprine 50 to 100 mg/day for several years, but she started to have worsening eye involvement, with ulceration to her left eye, as well as oral lesions and esophageal stricturing. She had low thiopurine methotransferase levels, which caused leukopenia on up-titration of the medication, thus necessitating usage of an alternative medication. She began receiving an infusion of rituximab at 10 mg/kg but experienced throat tightening, chest pain, and shortness of breath with the first infusion, even with premedication with acetaminophen, diphenhydramine, and methylprednisolone. She was subsequently treated with cyclophosphamide 50 mg/day but experienced notable fatigue after approximately 2 months of therapy. She also had intravenous immunoglobulin (IVIg) infusion during the course of 1.5 years, from 1.1 g/kg to 2 g/kg, but experienced itching, hypertension, nightmares, and hallucinations after several months of receiving treatment, which was thus discontinued.

On examination, the patient had significant conjunctival erythema with symblepharon in the right eye and ankyloblepharon and ocular surface keratinization of the left eye. Visual acuity was 20/70 in her right eye and hand motion in her left eye. The patient then began receiving corticotropin gel 80 units/mL subcutaneously twice a week as monotherapy. Two weeks after initiation of the medication, she had decreased conjunctival erythema, although she experienced a breakout on her skin to subcutaneous injections and so was transitioned

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to intramuscular injections, which she has tolerated. Her oral and esophageal symptoms cleared with IVIg and have remained stable while she receives corticotropin. During her treatment course, she developed a urinary tract infection and corticotropin gel was stopped for a few weeks. She experienced more discomfort and worsening eyesight during this time that resolved on restarting the medicine. Her most recent visual acuity was 20/40 in her right eye and light perception in her left. At her 18-month follow-up with the twice-weekly dosing, she had stable, controlled ocular disease without flare, with no noted oral involvement or eye tenderness.

DISCUSSION

Ocular cicatricial pemphigoid is a subepithelial autoimmune blistering disorder that is considered a subset or phenotype of mucous membrane pemphigoid. It commonly presents with bilateral ocular involvement, although one eye may be more affected. It usually manifests with chronic conjunctivitis and foreign-body sensation, leading to fibrosis and scarring. It can also lead to significant functional complications such as scar formation, trichiasis, corneal ulceration, and blindness. Diagnosis of ocular cicatricial pemphigoid depends on clinical suspicion and immunohistopathology of biopsied conjunctiva.[1] Conjunctival biopsies using immunofluorescence demonstrating linear deposition of immunoreactants (IgA, IgG, immunoglobulin M, and C3) at the basement membrane zone are necessary for definitive diagnosis of ocular cicatricial pemphigoid, although a negative biopsy result does not exclude the diagnosis.[1] There is currently no sensitive or specific laboratory test to establish diagnosis or monitor treatment for ocular cicatricial pemphigoid; indirect immunofluorescence assays have only a limited role in diagnosis, given a relatively low sensitivity of 52%.[1,2]

Treatment for ocular cicatricial pemphigoid is aimed at preventing scarring and potential complications, including blindness. Topical therapies are usually used as adjunct therapy with systemic therapy to prevent scarring. For mild to moderate ocular cicatricial pemphigoid, dapsone or methotrexate is usually the first-line treatment.[3] Other therapies for more resistant ocular cicatricial pemphigoid include mycophenolate mofetil, azathioprine, systemic corticosteroids, cyclophosphamide, IVIg, tumor necrosis factor-α inhibitors, and rituximab.[3] However, each systemic therapy has adverse effects that may preclude its usage. Our patient failed dapsone, mycophenolate mofetil, methotrexate, and azathioprine, in addition to having adverse effects with cyclophosphamide, rituximab, and IVIg. Thus, there was the need for alternative treatment to control her disease.

Adrenocorticotropic hormone is an endogenously produced melanocortin derived from the precursor molecule proopiomelanocortin protein, which is secreted from the anterior pituitary gland. It is part of the hypothalamic-pituitary pathway to stimulate glucocorticoid production from the adrenal cortex. Melanocortins not only stimulate endogenous glucocorticoid production but also have the ability to prevent nuclear factor-kappa B activation and inhibit synthesis and release of chemokines and cytokines, dampening host response to inflammation.[4] Corticotropin gel was approved by the Food and Drug Administration in 1952 for the treatment of autoimmune conditions; it is currently approved for conditions such as Steven-Johnson syndrome, rheumatoid arthritis, psoriatic arthritis, and sarcoidosis.[5] It has been shown to be effective in treating systemic lupus erythematosus[6] and dermatomyositis.[7] It is administered intramuscularly or subcutaneously and is well tolerated; potential adverse effects are similar to those of corticosteroids and include risk of infection, fluid retention, hypertension, glucose tolerance, and cushingoid features.

To date, there has been one case identified in the literature of a 75-year-old patient with ocular cicatricial pemphigoid who was either not responding to systemics or had other alternatives denied for coverage for ocular cicatricial pemphigoid and who was treated successfully with subcutaneous corticotropin injections twice weekly at 80 units/mL while receiving methotrexate 25 mg weekly.[5] To our knowledge, this is the first published case of ocular cicatricial pemphigoid treated with corticotropin injections as monotherapy. No major adverse effects have been appreciated. Although corticotropin injections are an expensive treatment and therefore not a first-line one, this case highlights an alternative treatment for patients with uncontrolled ocular cicatricial pemphigoid who have failed multiple other systemic immunosuppressants.

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