Treatment of severe perinuclear antineutrophil cytoplasmic antibody–associated vasculitis with efgartigimod

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INTRODUCTION

Antineutrophilic cytoplasmic antibody–associated vasculitis (AAV) is a heterogenous group of rare autoimmune disorders characterized by inflammation of small and medium-sized arteries. This inflammation can manifest in multiple organ systems including the kidneys, lungs, and skin. Cutaneous involvement of AAV most commonly presents with palpable purpura but can also cause a variety of dermatologic findings include vesicles, blisters, and necrotic-ulcerative lesions.[1] Cutaneous manifestations can be severe and are associated with life-threatening systemic manifestations including alveolar hemorrhage and glomerulonephritis.[1] Standard treatment for severe cutaneous AAV involves high-dose systemic corticosteroids in combination with rituximab or cyclophosphamide. In cases of severe progressive disease, plasmapheresis or intravenous immunoglobulin is initiated to facilitate rapid removal of antineutrophilic cytoplasmic antibody.[2] There are limited alternative therapeutic options for patients who do not respond adequately to conventional treatment. Newer therapies targeting the complement system include inhibitors of C5 (eculizumab), C5a (IFX-1), and the C5a receptor (avacopan), but their safety and efficacy, particularly for extrarenal manifestations, remain unclear.[3,4] However, efgartigimod, a neonatal Fc receptor antagonist, has shown promise as an immunomodulatory agent for the treatment of various autoimmune diseases, including myasthenia gravis and pemphigus vulgaris, with plans for a proof-of-concept trial for AAV expected in the coming year.[5,6]

We present a patient with perinuclear antineutrophilic cytoplasmic antibody positive vasculitis with severe refractory cutaneous and systemic disease treated with efgartigimod.

CASE REPORT

A 54-year-old woman with end-stage renal disease, hypertension, and pulmonary hypertension, all suspected to be secondary to her recent diagnosis of perinuclear antineutrophilic cytoplasmic antibody vasculitis, was admitted to the hospital for neck swelling and severe scleritis. She was not on systemic immunosuppression at the time of admission. Dermatology was consulted for multiple rashes, and she was found to have hemorrhagic bullae on the left hand, several edematous, purpuric wheals on the trunk and upper extremities, and a cluster of erythematous papules on the left oral commissure (Fig 1). She also reported hemoptysis dating back at least 1 year. Before admission, she was receiving hemodialysis 3 times weekly.

One year prior to admission, nephrology initiated a transplant work-up for her end-stage renal disease, revealing positive perinuclear antineutrophilic cytoplasmic antibody and elevated antimyeloperoxidase antibodies. However, the patient did not receive

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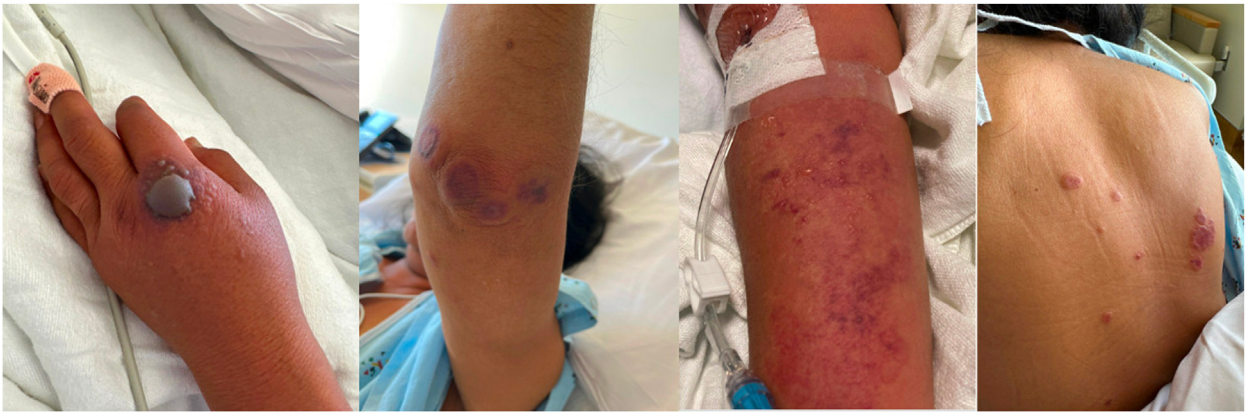

Fig 1. Bullae and purpuric wheals on the upper extremities and back on admission.

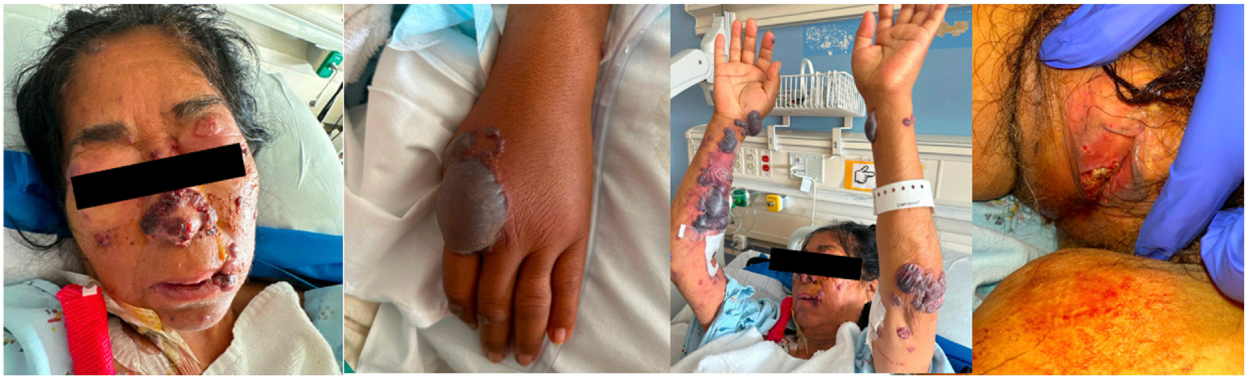

Fig 2. Progression of bullae on the face, upper extremities, and vagina despite methylprednisolone, cyclosporine, and plasmapheresis therapy.

follow-up care to address these pertinent findings. On admission, laboratory investigations revealed elevated inflammatory markers, with an erythrocyte sedimentation rate of 48 mm/h and C-reactive protein of 22.9 mg/dl. A skin punch biopsy confirmed cutaneous acute medium vessel vasculitis. Direct immunofluorescence of the tissue was negative.

She received a 1 g daily pulse dose of intravenous methylprednisolone for 3 days by rheumatology who thereafter managed the patient's immunosuppression regimen. However, the patient's cutaneous condition continued to progress, with an increase in the number and size of tender purpuric bullae on the skin and mucosal surfaces, including the tongue and vagina (Fig 2). Given continued aggressive cutaneous progression, cyclophosphamide and plasmapheresis were initiated on hospital day 5. Despite 3 doses of intravenous methylprednisolone 1 g, 4 doses of methylprednisolone 60 mg, 1 dose of intravenous cyclophosphamide 7.5 mg/kg, and 2 treatments of plasmapheresis, the patient's condition continued to deteriorate. She developed new bullae, increased chemosis of her eyes, and progressive difficulties swallowing due to the pain in her mouth from the blisters.

Given the degree of rapidly progressive cutaneous involvement indicating a poor prognosis, the decision was made to initiate off-label efgartigimod therapy after discussion with her rheumatology team. Efgartigimod was administered as an intravenous infusion once weekly at 10 mg/kg for 4 weeks. After the initiation of efgartigimod therapy, the patient's clinical condition began to rapidly improve. Two days after initial infusion, progression of the bullae halted, and many of the existing bullae decreased in size. Periorbital swelling decreased, and the patient reported improved cutaneous, oral, and vaginal pain (Fig 3). Her C-reactive protein continued to downtrend. The patient was transitioned to a prednisone taper of 1 mg/kg at 40 mg daily for 1 month followed by a taper of 30 mg daily for 2 weeks with a 5 mg reduction every 2 weeks thereafter. The patient is currently maintained on 15 mg of prednisone daily. Per the CYCLOPS protocol, she continued on intravenous cyclophosphamide infusions of 7.5 mg/kg every 2 weeks for

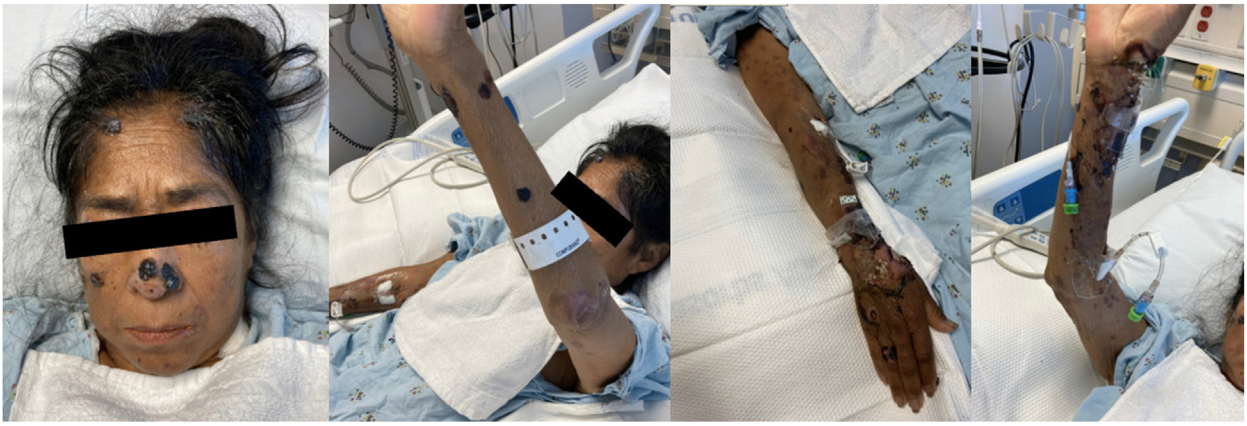

Fig 3. Cessation and improvement of bullae progression on the face and upper extremities after 3 doses of efgartigimod.

1 month followed by an infusion every 3 weeks where she remains for a planned total course of 8 months.[7] The patient tolerated the efgartigimod infusions well without any adverse reactions. She did develop new oral lesions after 1 dose of efgartigimod, and oral swab revealed herpes simplex virus-1 on polymerase chain reaction. The patient has had no further cutaneous flares since last follow-up 4 months following hospital discharge.

DISCUSSION

AAV is an autoimmune inflammatory disorder that can lead to direct destruction of vessel walls. Skin biopsies can support the diagnosis, exhibiting neutrophil-mediated vessel damage. Therefore, neutrophilic dermatoses such as Sweet syndrome could be considered, but Sweet syndrome has been shown to resemble small vessel neutrophilic vasculitis in approximately 29% of cases, typically with diffuse dermal involvement.[8] In all types of AAVs, cutaneous manifestations were associated with a poorer overall survival and relapse-free survival.[1]

High-dose systemic corticosteroids, followed by cyclophosphamide or rituximab, is the standard therapy in the treatment of AAV. However, median time to remission is 90 days or longer.[9] In patients with severe renal disease or refractory disease in other organs, plasmapheresis is recommended as an adjunctive therapy for more rapid removal of antineutrophilic cytoplasmic antibody to induce quicker remission.[2]

Efgartigimod is a human IgG1 antibody Fc-fragment that outcompetes endogenous IgG binding, reducing IgG recycling and increasing IgG degradation.[10] Trials using efgartigimod in myasthenia gravis led to significant reductions in all IgG subtypes, while those using this medication in pemphigus vulgaris and foliaceus demonstrated rapid disease control and complete clinical remission in a majority of patients when treated concurrently with prednisone.[5,6] With 1 dose of adjunctive efgartigimod therapy, our patient's progression of cutaneous manifestations halted, resulting in improved pain and inflammatory markers in addition to no new formation of bullae. It is important to note the patient had received additional fast-acting therapies (steroids, plasmapheresis) early in her treatment that may have also contributed to her improved clinical picture.

To our knowledge, this is the first reported case of AAV treated with efgartigimod. Overall, the patient experienced substantial improvement in the progression of her disease. She had no observed adverse event with the addition of efgartigimod. While the patient did develop oral herpes simplex virus-1 5 days after infusion of efgartigimod, she was on other immunosuppressive therapies before and after infusion, and previous studies have not observed an increased infection rate following exposure of any level with efgartigimod.[5,6,10] Efgartigimod may be a promising therapeutic option for AAV, particularly in patients with severe cutaneous manifestations. Further research and clinical trials are warranted to establish its role in the management of AAVs.

Conflicts of interest

None disclosed.

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