

Healing of Leg Ulcers Associated With Granulomatosis With Polyangiitis (Wegener Granulomatosis) After Rituximab Therapy

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PRACTICE POINTS

- Recognition of the dermatologic manifestations of granulomatosis with polyangiitis (GPA) may aid in an earlier diagnosis and appropriate treatment.
- Rituximab combined with corticosteroids may be a rapid and effective therapy for severe cutaneous ulcers related to GPA.

To the Editor:

A 52-year-old woman with a history of arthralgia, rhinitis, sinusitis, and episodic epistaxis was admitted to the hospital with multiple nonhealing severe leg ulcerations. She noticed subcutaneous nodules on the legs 6 months prior to the development of ulcers. The lesions progressed from subcutaneous nodules to red-black skin discoloration, blister formation, and eventually ulceration. Over a period of months, the ulcers were treated with several courses of antibiotics and wound care including a single surgical debridement of one of the ulcers on the dorsum of the right foot. These interventions did not make a remarkable impact on ulcer healing.

On physical examination, the patient had scattered 4- to 5-mm palpable purpura on the knees, elbows, and feet bilaterally. She had multiple 1- to 8-cm indurated purple ulcerations with friable surfaces and raised irregular borders on the feet, toes, and lower legs bilaterally (Figure, A–C).

One notably larger ulcer was found on the anterior aspect of the left thigh (Figure, A). Scattered 5- to 15-mm eschars were present on the legs bilaterally. She also had multiple large, firm, nonerythematous dermal plaques on the thighs bilaterally that measured several centimeters. There were no oral mucosal lesions and no ulcerations above the waist.

Magnetic resonance imaging of the foot showed some surrounding cellulitis but no osteomyelitis. Chest radiograph and computed tomography revealed bilateral apical nodules. Proteinase 3–antineutrophil cytoplasmic antibody (PR3-ANCA) testing was positive. Serum complement levels were normal. An antinuclear antibody test and rheumatoid factor were both negative. Skin biopsies were obtained from the thigh ulcer, foot ulcer, and purpuric lesions on the right knee. The results demonstrated leukocytoclastic vasculitis and neutrophilic small vessel vasculitis with necrotizing neutrophilic dermatitis and panniculitis. Granulomatosis with polyangiitis (GPA) was diagnosed based on these findings.

Initial inpatient treatment included intravenous methylprednisolone (100 mg every 8 hours for 3 doses), followed by oral prednisone 60 mg daily. Two weeks later the ulcers were reevaluated and only mild improvement had occurred with the steroids. Therefore, rituximab (RTX) was initiated at

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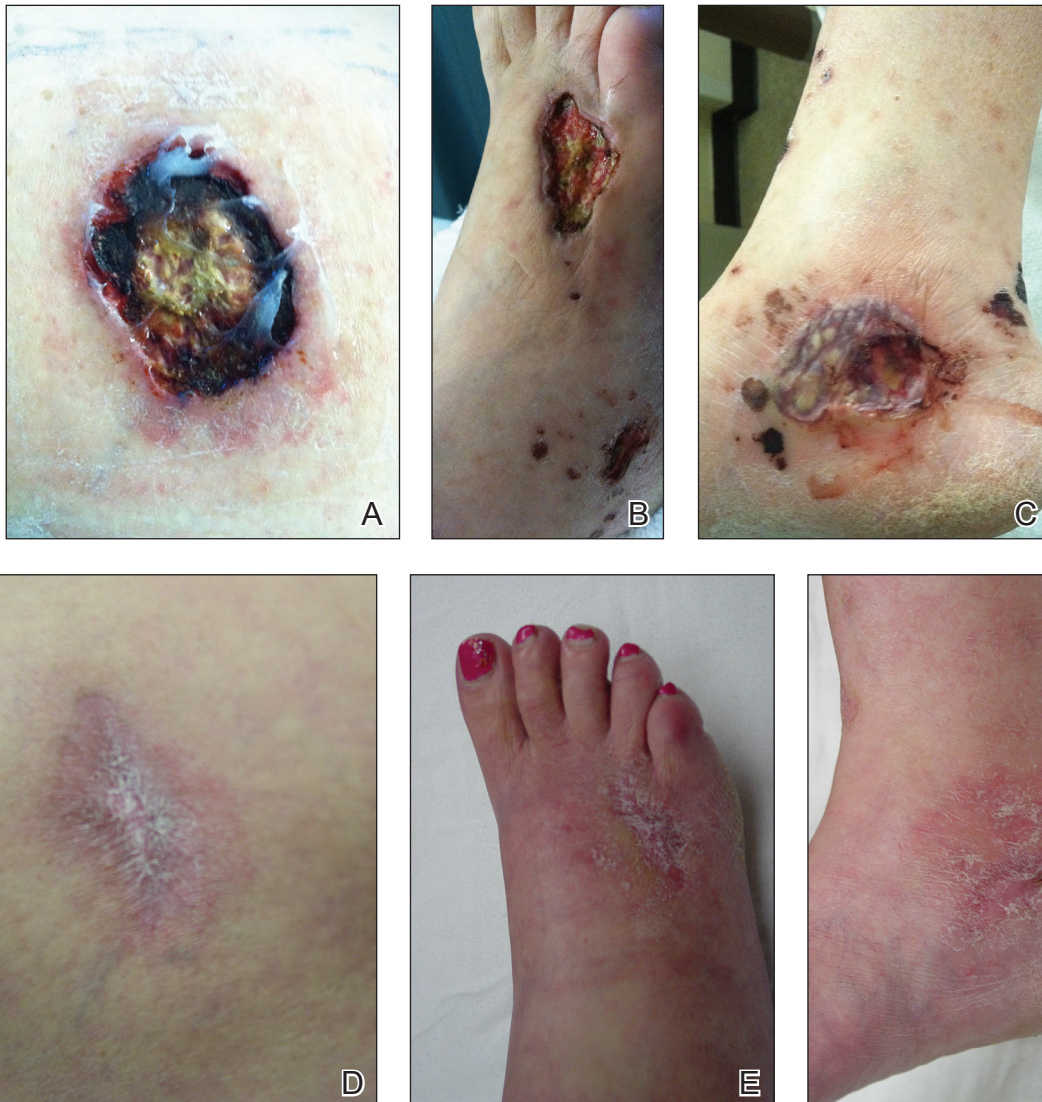
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375 mg/m² (700 mg) intravenously once weekly for 4 weeks. After 3 doses of RTX, the ulcerations were healing dramatically and the treatment was well tolerated. A rapid prednisone taper was started, and the patient received her fourth and final dose of RTX. Two months after the initial infusion, the thigh ulcer and most of the ulcerations on the feet and lower legs had almost completely resolved. Photographs were taken 5 months after initial RTX infusion (Figure, D–F). A chest radiograph 4 months after initial RTX infusion showed resolution of lung nodules. Two months after RTX induction therapy, azathioprine was added for maintenance but was stopped due to poor tolerance. Oral methotrexate

17.5 mg once weekly was added 5 months after RTX for maintenance and was well tolerated. At that time the prednisone dose was 10 mg daily and was successfully tapered to 5 mg by 9 months after RTX induction therapy.

Granulomatosis with polyangiitis (Wegener granulomatosis) is a granulomatous small- and medium-sized vessel vasculitis that traditionally affects the upper and lower respiratory tract and kidneys.¹ Skin lesions also are quite common and include palpable purpura, ulcers, vesicles, papules, and subcutaneous nodules. Patients with active GPA also tend to have ANCA directed against proteinase 3 (PR3-ANCA). Although GPA was



Anterior thigh (A), dorsum of the foot (B), and ankle (C) before and 5 months after the initial rituximab infusion (D, E, and F, respectively).

once considered a fatal disease, treatment with cyclophosphamide combined with corticosteroids has been shown to substantially improve outcomes.¹ Rituximab, a chimeric monoclonal anti-CD20 antibody, works by depleting B lymphocytes and has been used with success to treat diseases such as lymphoma and rheumatoid arthritis.^{2,3} The US Food and Drug Administration approved RTX for GPA and microscopic polyangiitis in 2011, with a number of trials supporting its efficacy.⁴

The success of RTX in treating GPA has been documented in case reports as well as several trials with extended follow-up. A single-center observational study of 53 patients showed that RTX was safe and effective for induction and maintenance of remission in patients with refractory GPA. This study also uncovered the potential for predicting relapse based on following B cell and ANCA levels and preventing relapse by initializing further treatment.⁵ Other small studies and case reports have shown similar success using RTX for refractory GPA.⁶⁻¹⁰ These studies included various combinations of concurrent therapies and various follow-up intervals. The Rituximab in ANCA-Associated Vasculitis (RAVE) trial compared RTX versus cyclophosphamide for ANCA-positive vasculitis.¹¹ This multicenter, randomized, double-blind study found that RTX was as efficacious as cyclophosphamide for induction of remission in severe GPA. The data also suggested that RTX may be superior for relapsing disease.¹¹ Another multicenter, open-label, randomized trial (RITUXVAS) compared RTX to cyclophosphamide in ANCA-associated renal vasculitis. This trial also found the 2 treatments to be similar in both efficacy in inducing remission and adverse events.¹²

Some conflicting reports have appeared on the effectiveness of using RTX for the granulomatous versus vasculitic manifestations of GPA. Aires et al¹³ showed failure of improvement in most patients with granulomatous manifestations of GPA in a study of 8 patients. A retrospective study including 59 patients who were treated with RTX also showed that complete remission was more common in patients with primarily vasculitic manifestations, not granulomatous manifestations.¹⁴ However, some case series that included patients with refractory ophthalmic GPA, a primarily granulomatous manifestation, have found success using RTX.^{15,16} More studies are needed to determine if there truly is a difference and whether this difference has an effect on when to use RTX. The skin lesions our patient demonstrated were due to the vasculitic component of the disease, and consequently, the rapid and complete response we observed would be consistent with the premise that the therapy works best for vasculitis.

Most of the trials assessing the efficacy of RTX utilize a tool such as the Wegener granulomatosis–specific Birmingham Vasculitis Activity Score.¹⁷ This measure of treatment response does include a skin item, but it is part of the composite response score. Consequently, a specific statement regarding skin improvement cannot be made. Additionally, little is reported pertaining to the treatment of skin-related findings in GPA. One report did specifically address the treatment of dermatologic manifestations of GPA utilizing systemic tacrolimus with oral prednisone successfully in 1 patient with GPA and a history of recurrent lower extremity nodules and ulcers.¹⁸ The efficacy of RTX in limited GPA was good in a small study of 8 patients. However, the study had only 1 patient with purpura and 1 patient with a subcutaneous nodule.¹⁹ Several other case series and studies have included patients with various cutaneous findings associated with GPA.^{5,7,9,11} However, they did not comment specifically on skin response to treatment, and the focus appeared to be on other organ system involvement. One case series did report improvement of lower extremity gangrene with RTX therapy for ANCA-associated vasculitis.⁸ Our report demonstrates a case of severe skin disease that responded well to RTX. It is common to have various skin findings in GPA, and our patient presented with notable skin disease. Although skin findings may not be the more life-threatening manifestations of the disease, they can be quite debilitating, as shown in our case report.

Our patient with notable leg ulcerations required hospitalization due to GPA and received RTX in addition to corticosteroids for treatment. We observed a rapid and dramatic improvement in the skin findings, which seemed to exceed expectations from steroids alone. The other manifestations of the disease including lung nodules also improved. Although cyclophosphamide and corticosteroids have been quite successful in induction of remission, cyclophosphamide is not without serious adverse effects. There also are some patients who have contraindications to cyclophosphamide or do not see successful results. In our brief review of the literature, RTX, a B cell–depleting antibody, has shown to have success in treating refractory and severe GPA. There is little reported specifically about treating the skin manifestations of GPA. A few studies and case reports mention skin findings but do not comment on the success of RTX in treating them. Although the severity of other organ involvement in GPA may take precedence, the skin findings can be quite debilitating, as in our patient. Patients with GPA and notable skin findings may benefit from RTX, and it would be beneficial to include these results in future studies using RTX to treat GPA.

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