Adalimumab Treatment for Pyoderma Gangrenosum

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF A CASE

A 47-year-old woman was referred to Washington University dermatology clinic for a nonhealing ulcer on her right shin of 8 months’ duration. She reported having had a similar ulcer on her left shin 6 years ago. The patient’s medical history was significant for non–insulin-dependent diabetes mellitus, hypertension, and osteoarthritis. On examination, she was found to have a 2 × 3-cm punched-out ulcer with rolled borders on her right shin. Evaluation of a biopsy specimen taken 6 months prior to presentation showed extensive dermal necrosis with ulceration and abscess formation and microangiopathy manifested by thickening of the capillary walls with fibrinous deposits and microthrombi. The overall histologic findings were thought to be most consistent with atrophie blanche.

Further evaluations at presentation included a complete blood cell count with differential and rheumatoid factor, both of which were within normal limits. She had no reaction to purified protein derivative. A routine tissue culture grew rare Enterococcus species. After 1 month of therapy with minocycline, 100 mg orally, twice daily, and Unna wraps with application of clobetasol 0.05% ointment, a second biopsy specimen taken 6 months prior to presentation showed extensive dermal necrosis with ulceration and abscess formation and microangiopathy manifested by thickening of the capillary walls with fibrinous deposits and microthrombi. The overall histologic findings were thought to be most consistent with atrophie blanche.

A systemic treatment was needed.

CLINICAL CHALLENGE

There is no universally accepted treatment for PG and no therapy has been subjected to a controlled clinical trial. In mild disease, therapy consists of local wound care and topical or intralosal corticosteroids. For more severe disease, systemic agents are necessary. These include steroid-sparing agents such as sulfasalazine, dapsone, clofazimine, and other antibiotics. Systemic corticosteroids are often effective, but large doses are required leading to serious long-term adverse effects. Other immunosuppressive agents such as cyclosporine, infliximab, etanercept, tacrolimus, mycophenolate mofetil, methotrexate, azathioprine, mercaptopurine, and cyclophosphamide have been reported to be successful in individual case reports and small case series. However, they too are associated with significant toxic effects.

Aggressive topical therapy had failed to help this patient. Treatment with systemic corticosteroids or cyclosporine in a patient with diabetes mellitus and hypertension was believed to be too risky. Consequently, an alternative therapy was needed.

SOLUTION

Adalimumab (Humira; Abbott Laboratories, Abbot Park, Ill) was proposed as an alternative to systemic corticosteroids, cyclosporine, and other immunosuppressive agents. Adalimumab was administered subcutaneously at a dose of 80 mg/wk for the first 2 weeks followed by 40 mg/wk. The patient continued to be treated with Unna wraps with clobetasol 0.05% ointment for the first 3.5 months. Objective clinical improvement could be seen after 2 months of therapy. After 3.5 months of therapy, the ulcer was nearly healed with only a 1.7 × 0.7-cm shallow area of ulceration remaining (Figure 2). After 5.5 months of therapy, the ulcer was nearl...
ulcer was completely healed (Figure 3). The patient did not experience any adverse events.

**COMMENT**

Pyoderma gangrenosum is an uncommon neutrophilic dermatosis that consists of nodules and pustules that ulcerate. Pyoderma gangrenosum can occur anywhere on the body, including the mouth, genitalia, and around ileostomy and colostomy sites in patients with ulcerative colitis and Crohn disease who have had abdominal surgery. Lesions often progress in size and may be multiple. Complications include severe pain, scarring, secondary infection, and extracutaneous involvement. Some patients have accompanying fever, malaise, arthralgias, and myalgias. Pyoderma gangrenosum is associated with autoimmune disorders such as inflammatory bowel disease, seronegative arthritis, and rheumatoid arthritis. It is also associated with leukemic and preleukemic states and paraproteinemias. The pathogenesis of PG is unknown, but its association with autoimmune disorders and the phenomenon of pathergy that occurs in PG suggests that disturbances in immune regulation are involved.

Tumor necrosis factor α (TNF-α) is a proinflammatory cytokine that is produced by macrophages, lymphocytes, and neutrophils. It is known to induce other proinflammatory cytokines such as interleukin (IL)-1, IL-6, and IL-8. Tumor necrosis factor α also acts on the endothelium to promote leukocyte migration into sites of inflammation. Increased levels of TNF-α are found in patients with rheumatoid arthritis and Crohn disease, which are associated with PG. Inhibition of TNF-α-induced inflammation could effectively treat PG.

This hypothesis is supported by a review of the Medline database from 1966 to the present, which revealed 15 case reports and case series of successful treatment of PG with infliximab. Infliximab is a chimeric, monoclonal antibody directed against TNF-α and is currently approved by the US Food and Drug Administration to treat rheumatoid arthritis and Crohn disease.

In the largest case series, 13 patients with inflammatory bowel disease and PG were successfully treated with infliximab at a dose of 5 mg/kg. Patients received a mean of 9.8 cycles (range, 1-24 cycles). In this retrospective study, 3 patients had a complete response to induction infliximab therapy and did not require additional treatment. Ten patients responded to induction infliximab treatment and maintained healing with infusions every 4 to 12 weeks. The mean time to a clinical response was 11 days (range, 2-30 days). The mean time to complete healing was 86 days (range, 7-210 days). All patients receiving corticosteroids were able to discontinue treatment with them completely after institution of infliximab treatment. However, 11 patients remained under treatment with azathioprine and mercaptopurine. The only reported adverse events were sunburn in one patient and an infusion reaction in another.

In the second largest case series, Ljung et al treated 8 patients with Crohn disease and PG with infliximab, 5 mg/kg. The authors do not specify whether additional treatments were used. Three patients experienced complete healing after 2 to 3 cycles. One of these patients discontinued therapy owing to development of a rash. A fourth patient experienced complete healing after 6 months but later relapsed. This patient developed severe pneumonia, which prevented further treatment. A fifth patient had near complete healing after 3 cycles, but treatment was withdrawn secondary to development of fever, abdominal pain, and diarrhea. Two patients had a partial response. One patient had no improvement.

This is, to our knowledge, the first report of successful treatment of PG with adalimumab, which is the first fully human monoclonal antibody directed against TNF-α. It possesses high specificity and affinity for TNF-α (kDa=6×10^{-10} M) and blocks the interaction of TNF-α with the p55 and p75 cell surface TNF receptors. Like infliximab, adalimumab fixes complement and lyses surface TNF-expressing cells in vitro. Adalimumab is indistinguishable from naturally occurring human IgG1 and therefore
has a half-life comparable to human IgG1, approximately 2 weeks.21

Given that adalimumab targets the same cytokine as infliximab, one would expect that adalimumab might also be effective in the treatment of PG. The effectiveness of adalimumab in the treatment of PG is demonstrated in this case. Our patient responded to therapy in 2 months and had complete healing after 5.5 months of treatment. Patients who have been treated with infliximab tend to respond after 1 to 3 cycles.5-20 The time to complete healing varies considerably, as demonstrated in the study by Regueiro et al,10 and depends on the extent of disease. Comparison of time to response to treatment between adalimumab and infliximab is made more difficult by the fact that patients who have been treated with infliximab often receive concomitant therapy with systemic immunosuppressive agents, whereas our patient did not.

Treatment with adalimumab is advantageous over infliximab through differences in drug delivery. Adalimumab is administered subcutaneously once weekly or every other week by the patient at home, which most patients find to be convenient. Patients can be instructed on proper injection technique during 1 nurse visit. In- fliximab, by contrast, is delivered intravenously in the office. This requires routine office visits and vital sign monitoring by a health care professional. Infusion reactions such as allergic reactions (pruritus and urticaria) occur in about 9% of patients.22 The time to response to infliximab in patients with rheumatoid arthritis in a clinical practice setting: relationship to dose, antihistamine pretreatment, and infusion-related reactions to infliximab in patients with rheumatoid arthritis. J Inflamm. 2003;6:40-424.


References


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