Poor Prognosis of Arthritis-Associated Pyoderma Gangrenosum

Carlos A. Charles, MD; Tracy L. Bialy, MD, MPH; Anna F. Falabella, MD; William H. Eaglstein, MD; Francisco A. Kerdel, MD; Robert S. Kirsner, MD

Background: The association between pyoderma gangrenosum (PG) and arthritis is well established. We have observed a refractory population of patients with arthritis-associated PG (PGA). We, therefore, tested the hypothesis that differences exist in response to treatment in patients with PGA compared with patients with PG without arthritis.

Observations: We performed a review of patients with PG during a 2-year period. Patients had noninfectious chronic ulcerations clinically typical for PG, exclusion of relevant differential diagnoses, and consistent histopathological features. Outcomes compared between patients with arthritis (PGA) and without arthritis (PG) included complete healing, percentage change in wound size, and duration of therapy. Of 10 PG ulcers, 7 healed, compared with 2 of 8 PGA ulcers. There was a greater mean percentage decrease in wound size in the PG vs the PGA ulcers (78.9% vs 23.4%; \(P = 0.10\)) and a shorter mean duration of treatment (8.7 vs 14.8 months; \(P = 0.18\)).

Conclusions: The ulcers of patients with PGA seem more refractory to treatment than the ulcers of patients with PG alone. Those with PGA ulcers represent a refractory subset of patients, and the ulcers are possibly secondary to unique pathophysiological features.

Arch Dermatol. 2004;140:861-864
Eighteen patients met the inclusion criteria for PG and were included in our study. Of the 18 patients, 8 had PG and the other 10 had PG not associated with arthritis. Patients were seen and followed up for a mean of 12.1 months (SD, 9.6 months), with a range of 1 to 24 months. For consistency of comparison, only patients treated for ulcers located on their lower extremities were enrolled. Patients with PG were similar to patients with PG alone with regard to age, race, sex, size of the ulcer pretreatment, and histologic features (Table 2).

We found differences between the treatment response of the 2 groups. Of the 10 PG ulcers, 7 healed, compared with 2 of the 8 arthritis-associated PG (PGA) ulcers (Figure 1). While the ulcer size between groups was similar before treatment, the PG ulcers were significantly smaller than the PGA ulcers after treatment. In addition, the mean ulcer size after treatment was significantly smaller in the patients with pyoderma gangrenosum (PG) (P=.01), while the arthritis-associated PG (PGA) ulcers did not demonstrate a significant (P=.54) response. Because a reduction in wound size represents a good prognostic factor for other long-term wounds, such as venous ulcers, we compared ulcers that decreased by greater than 50% during the treatment period. We found that 8 of the 10 PG ulcers decreased by greater than 50%, compared with 3 of the 8 PGA ulcers (Figure 4).

**RESULTS**

PG. These include clinical criteria (painful ulceration, an undermined border, surrounding erythema, a purulent base, and rapid onset and enlargement) and histologic criteria (epidermal necrosis/ulceration, superficial dermal edema, and a dense, neutrophilic, and mixed dermal/subcutaneous infiltrate). Patients had noninfectious chronic ulcerations clinically typical for PG and the exclusion of relevant differential diagnoses through biopsy, tissue culture, and appropriate laboratory studies. If a patient had multiple ulcers, the target lesion was defined as the largest ulcer. Treatment measures other than prednisone included cyclosporine, intraleisional triamcinolone acetonide, minocycline, doxycycline, granulocyte-macrophage colony-stimulating factor, oral tacrolimus, and colchicine (Table 1). Outcomes compared between patients with PG and those with PGA included complete healing, percentage change in wound size, and duration of therapy. Arthritis was defined as one or more of the following findings: rheumatoid factor positive, physical findings of arthritis, or arthritis by medical history. Percentage change in wound size represents a good prognostic factor for other long-term wounds, such as venous ulcers, we compared ulcers that decreased by greater than 50% during the treatment period. We found that 8 of the 10 PG ulcers decreased by greater than 50%, compared with 3 of the 8 PGA ulcers (Figure 4).

**Abbreviations:** PG, pyoderma gangrenosum; PGA, arthritis-associated PG.
We describe a refractory subset of patients with PGA. The association between PG and arthritis is well established, and has included various types of arthritis. Classic seronegative rheumatoid arthritis (RA); an unusual, progressive, erosive, seronegative arthritis that is not associated with HLA-B27, psoriasis, or Reiter syndrome; and a seronegative arthritis associated with inflammatory bowel disease have all been associated with PG.\(^7\) Also, seronegative HLA-B27–positive spondyloarthopathies have been reported in association with PG.\(^10\) In the 18 patients studied retrospectively in this report, 10 had PG alone while 8 presented with PGA. Although other series\(^8\) have described up to 37% of patients with PG being associated with arthritis, the large percentage of PGA patients in the present series may be because of a referral bias inherent to our university-based clinic, due to either a more difficult to diagnose or a more refractory subset of patients.

To better compare outcomes, we compared ulcers in patients with PG and PGA that occurred on the lower extremities. Pyoderma gangrenosum commonly presents on the lower extremities,\(^4\) and patients with RA are also predisposed to developing leg ulcerations.\(^11\) Several possible explanations may account for why patients with PGA represent a more refractory subset. Concomitant disease present in patients with PGA may be partially to blame. The presence of decreased ankle range of motion in patients with arthritis, in general, is associated with venous insufficiency,\(^12\) the most common cause of chronic leg ulcers. Alternatively, patients with PGA may have distinct pathophysiological features. The basis of the lower leg predilection for ulceration of PG- and RA-associated ulcers has not been completely elucidated; however, there are several identifiable factors present in patients with RA that may lead to this phenomenon. Factors such as skin fragility, arterial disease, peripheral edema, nutritional status, and, most important, venous insufficiency may all predispose patients with RA to leg ulcerations.

Patients with arthritis are at an increased risk for developing venous insufficiency because of their immobility, impaired fibrinolysis,\(^13\) and poor calf muscle pump function due to ankle arthritis and muscle atrophy.\(^14\) In fact, a study by McRorie et al\(^14\) assessed the venous function, arterial pressures, and range of ankle movement in 23 patients with RA with a leg ulcer, and compared the results with those in the nonulcerated contralateral limb and in 25 patients with RA matched for age and duration of arthritis. They found evidence of venous insufficiency in the patients with RA and ulcer compared with control subjects. In addition, ankle movement was more restricted in the ulcerated limb compared with the nonulcerated contralateral limb. There was no difference in large-vessel arterial function between groups. These findings suggest that venous insufficiency may play a fundamental role in the development and progression of leg ulcers for patients with RA, and may play a critical role in the refractory nature of leg ulcers for PGA patients.

Because the differential diagnosis of PG is expansive, it remains possible that in the setting of concomitant seronegative or seropositive arthritis, the inflammatory process associated with arthritis may be causal in these patients’ ulcers, representing a unique entity. In addition, a combination of factors, including PG and arthritis, may also be at play. Interestingly, cutaneous ulcerations secondary to arthritis are known to be particularly resistant to treatment and associated with a great deal of morbidity.\(^15\)

While this report demonstrates the refractory nature of PGA ulcers, there are inherent limitations to this case study. First, only 18 patients met the inclusion criteria and were studied. Second, as previously stated, the patients studied in this report were all taken from a referral-based university wound care center.

In conclusion, we describe a refractory subset of patients with PGA. This may be either related to concomitant disease or possibly secondary to unique pathophysiological features.
References


News and Notes

A Study of Nonmelanoma Skin Cancer in Organ Transplant Recipients

We at the University of California, San Francisco (UCSF), are embarking on a National Institutes of Health–funded study of why organ transplant recipients are so susceptible to nonmelanoma skin cancers. Integral to our research is the establishment of a collection of specimens, a “Tissue Bank,” which will serve not only our own investigations but which we hope also will become a shared resource available to others.

Specifically, we need (1) blood samples for DNA extraction from organ transplant recipients with nonmelanoma skin cancers and (2) tumor samples (blocks) from this patient group. Our studies are approved by the UCSF Committee on Human Research, and local institutional review board approval should not be necessary if the patients contact us directly.

We would be delighted to hear from any interested patients or physicians at 866-386-8500; epsteine@derm.ucsf.edu; or San Francisco General Hospital, 1001 Potrero Ave, Room 269, Bldg 100, San Francisco, CA 94110.