Progression of pyoderma gangrenosum with angioinvasive fungus

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Pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis that classically manifests as painful, rapidly evolving, violaceous ulcers that display pathergy.[1] The etiology of PG is poorly understood, but inflammatory cytokines, such as tumor necrosis factor α, interleukin 1 (IL-1), and IL-17, have been implicated in the pathogenesis of this disorder.[2,3] Biologic immunomodulators targeting inflammatory cytokines have shown great potential for the treatment of autoimmune diseases such as rheumatoid arthritis and lupus erythematosus. Recent studies have demonstrated that these agents are also effective in some PG cases.[4] Although many PG patients will recover with standard therapy, treatment with combination immunomodulators may be necessary for patients who are suffering from severe chronic or relapsing PG lesions. However, treatment with immunosuppressive agents requires finding the appropriate balance between suppressing inflammation and avoiding opportunistic infection.[5]

Anakinra is an IL-1 receptor antagonist that has been used for treatment of several autoimmune disorders.[6] IL-1 is an innate proinflammatory cytokine that binds the IL-1 receptor to promote inflammation and recruitment of immune cells.[6] Inhibition of IL-1 broadly reduces inflammation but may also prevent a proper immune response to pathogens. It is estimated that 1% to 10% of patients treated with anakinra will suffer from a severe infection.[5,7] In patients with recalcitrant immune diseases, anakinra should be added with care, particularly in the setting of concomitant immunosuppressants.

Abbreviations used:

AIF: angioinvasive fungus
IL: interleukin
PG: pyoderma gangrenosum

CASE REPORT

A 64-year-old woman with a history of hypertension, diabetes mellitus, and vitiligo presented to our clinic for treatment of biopsy-proven PG that had been present for over a year. At the time of presentation, she had a single large ulcer with a violaceous border on the lower portion of her left leg. The workup for malignancy and for other autoimmune diseases was negative. She presented without any systemic complaints. Her PG was refractory to several standard treatments over the course of a year, including prednisone, cyclosporine, and doxycycline. She also did not respond to adalimumab but had responded to infliximab infusions combined with cyclosporine. She was treated topically with vinegar soaks, tacrolimus cream, and fluocinonide ointment. She had daily dressing changes and care by a wound care specialist. Her ulcer subsequently improved. However, her improvement plateaued at 10 months, and the lesion appeared to be progressing (Fig 1, *A*). To stop any further disease progression, which might have been from loss of response secondary to neutralizing antibodies to infliximab, she was switched to anakinra, 100 mg daily. Her dose of cyclosporine was continued with plans to stop if the lesion improved. She was continued on the topical regimen described above. Initially, her 1-month follow-up showed improvement (Fig 1, *B*), and anakinra was continued along with the rest of her regimen. However, 2 months after starting anakinra, she reported pain in her leg and felt that the lesion was progressing again. Her follow-up visit at 3 months after starting anakinra revealed that her

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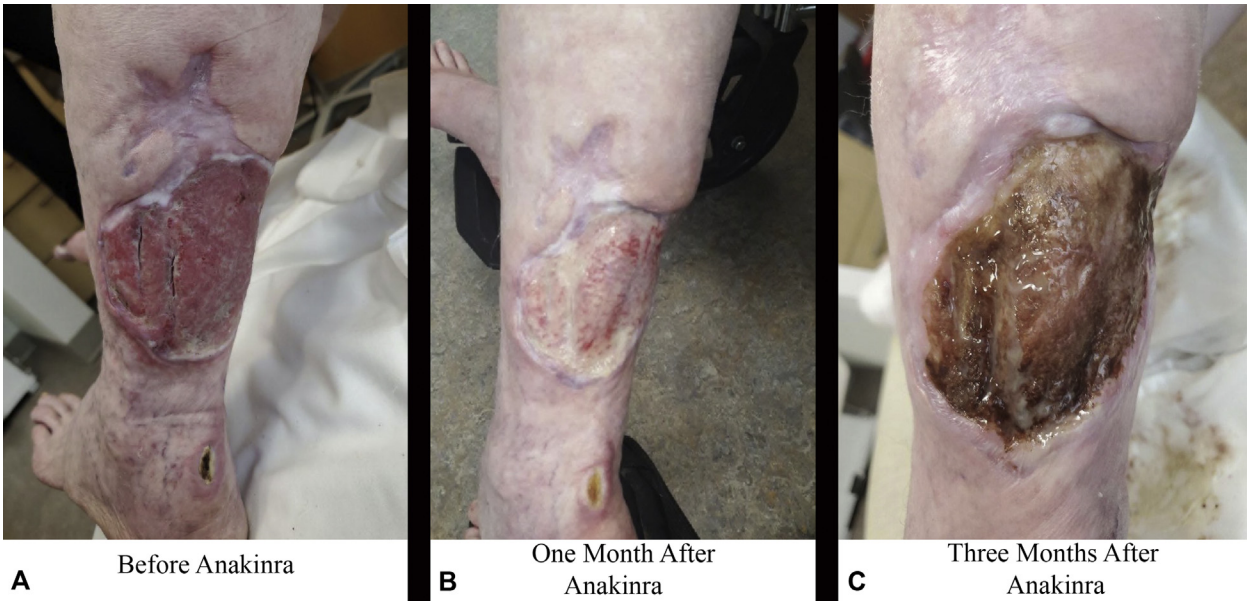

Fig 1. Reduction and then progression of lesion on the left lower extremity. **A**, Lesion arrested in progression. **B**, Gradual re-epithelialization after 1 month of anakinra and cyclosporine treatment. **C**, Development of eschar and necrotic borders after 3 months of anakinra and cyclosporine treatment.

ulcer had developed a golden-yellow eschar with a black necrotic perimeter (Fig 1, *C*). Because of concern for superimposed infection, a biopsy specimen was obtained from this necrotic area, which revealed an angioinvasive fungus (AIF) that was cultured to yield several *Mucor* species (Fig 2). She was promptly started on antifungal treatment with posaconazole and underwent debridement of the wound. However, because of the extensive progression of the infected ulcer, she underwent below-the-knee amputation. She was treated with a wound vacuum and posaconazole postoperatively and has not had recurrence of her PG since amputation.

DISCUSSION

PG is a neutrophilic dermatosis characterized by painful ulcers that display pathergy.[1,8] The classic variant of PG usually starts as a small, painful papule that can be mistaken for an insect bite and often occurs on the legs.[8] The lesion widens, deepens, and becomes an ulcer with a marked overhanging gray or violaceous edge. The diagnosis of PG can be challenging and requires exclusion of other ulcerative pathologies.[9] Biopsy is advised but may fail to show the distinctive neutrophilic infiltration that would raise suspicion for this diagnosis. Although PG is a poorly understood disorder, most patients recover when properly treated. Current therapy consists of a combination of local wound care, anti-inflammatory drugs, antibacterial agents, and immunosuppressants.[1,3]

Newer and more specific biologic treatments, such as infliximab, adalimumab, etanercept, ustekinumab, canakinumab, and anakinra, target proinflammatory chemokines and have had promising results in patients with complicated PG.[10] However, the use of immunosuppressant agents (biologics and other systemics) predisposes patients to opportunistic infections, including AIF.[10] The most frequently isolated AIFs in clinical practice are *Candida, Cryptococcus, Aspergillus, Mucormycetes*, and *Fusarium*. Treating AIF requires identification of the fungal species, initiation of appropriate antifungal medications, and surgical debridement. Even with aggressive management, AIF has a poor prognosis and can rapidly spread if not detected early. Therefore, AIF should be a consideration in patients whose condition is clinically deteriorating.

The use of anakinra for PG has been reported but remains rare in the literature.[4,10] This treatment had promising results in our patient with a severely recalcitrant ulcer with a duration of more than a year. However, this case involved an important complication in the management of PG requiring immunosuppression. Our patient was being treated with 2 immunosuppressants, cyclosporine and anakinra, and was therefore less able to mount an immune response. We were in the process of bridging the patient to anakinra, and her complication occurred at an especially vulnerable point in her care. Because she had had numerous flares previously, we were reluctant to transition rapidly to

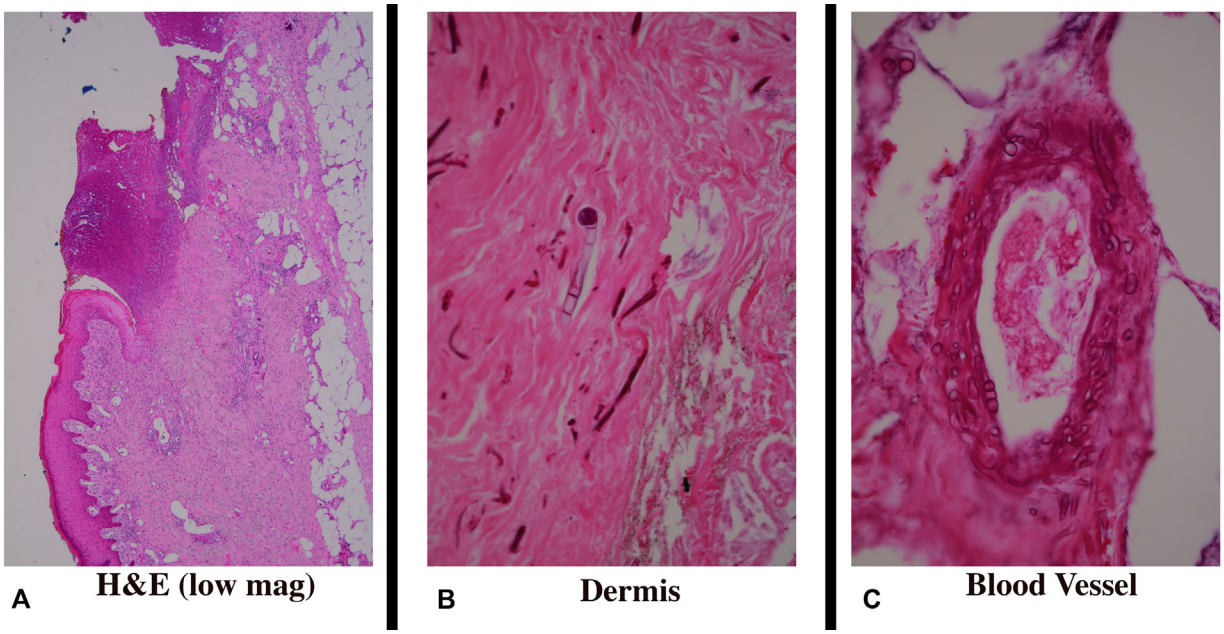

Fig 2. Histologic findings of skin biopsy. Sections obtained from local excision of the skin on the left lower extremity showed angioinvasive fungal infection. The skin and subcutaneous tissue showed ischemic changes and necrosis (**A**). Dermis and subcutaneous fat adjacent to the necrosis (**B**) and thrombosed vessels (**C**) showed fungal hyphae. (Hematoxylin-eosin stain)

monomodal anakinra and planned to taper her cyclosporine over time. Repeat biopsy of her worsening plaque revealed AIF and required an immediate change in her treatment. This finding highlights the need to consider broadly any sudden change in clinical course in a patient whose condition is improving. Patients with complicated PG are commonly iatrogenically immunosuppressed and have a break in the skin barrier, which makes them particularly susceptible to infections. Because of the exuberant inflammatory dysregulation, potent immunosuppressants, often in combination as described in our case, are necessary to attenuate the severely abnormal immune response. Therefore, patients with PG who are treated with anakinra (especially those on multimodal immunosuppression) require special attention, frequent surveillance, and a low threshold for biopsy if they have unexplained worsening of their disease.

Conflicts of interest

None disclosed.

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