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Use of Becaplermin for nondiabetic ulcers: pyoderma gangrenosum and calciphylaxis

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Abstract

Large difficult to heal ulcers of various etiologies carry a high morbidity and mortality rate. Becaplermin is a recombinant platelet-derived growth factor approved for treatment of diabetic ulcers. In this two-case series, we report the use of becaplermin in the treatment of ulcers due to (i) calciphylaxis, an often fatal condition resulting from systemic calcification and thrombosis of vessels and (ii) pyoderma gangrenosum (PG), a neutrophilic dermatosis. We also report that topical collagenase worsened PG ulcers, consistent with pathergy. Becaplermin can be used to help treat ulcers resulting from calciphylaxis and PG. These encouraging results lend support for the utilization of becaplermin in the treatment of nondiabetic chronic ulcers of various etiologies.

Keywords

becaplermin; calciphylaxis; pyoderma gangrenosum

Introduction

Pyoderma gangrenosum (PG) is an uncommon neutrophilic dermatosis that is diagnosed clinically in conjunction with compatible histology (1). Lesions begin as painful pustules, bullae, or fluctuant nodules that evolve into ulcers with a violaceous mucopurulent base. In 50% of cases, PG is associated with systemic diseases like arthritis, inflammatory bowel disease, hepatitis, monoclonal gammopathies, hematologic malignancies, and immunodeficiencies (2). PG in association with IgA paraproteinemia in particular has been reported in 10–18% of patients (3). PG can have extra-cutaneous manifestations, most commonly pulmonary nodules that may have central caseation with biopsies revealing nonspecific necrotizing inflammatory granulomas with sterile neutrophilic infiltrates (4,5). Standard treatment involves immune modulation, typically through the use of systemic

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Conflict of interest

None of the authors have any conflicts of interest.

Ethics

Informed consent was obtained for all images in this manuscript.

steroids. Here, we present an interesting case of PG with pulmonary involvement that worsened with topical collagenase and improved with topical becaplermin (a topical platelet-derived growth factor (PDGF)).

Furthermore, we present a case of calciphylaxis treated with becaplermin. Calciphylaxis is a rare, often fatal condition that results from systemic calcification and thrombosis of small to medium sized vessels (6). It is most commonly associated with renal failure, particularly those on hemodialysis (7). However, it has been observed in nonuremic patients with hyperparathyroidism, liver disease, trauma, connective tissue disease, hypercoagulability, and infections like HIV (8). Calciphylaxis presents with painful mottled lesions that evolve into nonhealing necrotic gangrenous ulcers usually on the digits or lower extremities. Histopathological findings include calcification and thrombosis of medium-sized vessels, ulcerations, tissue necrosis, and panniculitis (8). Treatments that have previously been described include parathyroidectomy, cinacalcet, corticosteroids, thrombolytics, heparin, bisphosphonates, and hyperbaric oxygen (7).

This two case series highlights the utility of becaplermin, a homodimeric recombinant topical PGDF approved by the FDA in 1997 for treatment of uninfected diabetic foot ulcers with adequate vascular supply that extend into the subcutaneous tissue (9).

Report of cases

Case 1

A 79-year-old male with history of monoclonal gammopathy of undetermined significance (MGUS) developed night sweats and occasional hemoptysis without skin lesions. A computed tomography scan showed mass-like pulmonary consolidations with cavitation and hilar lymphadenopathy. Lung biopsy showed acute inflammation and necrosis with negative infectious stains and no evidence of malignancy.

Six-months later, the patient presented with an “inflamed cyst on the right knee” that was incised and drained. The lesion continued to worsen despite cephalexin and amoxicillin/clavulanate, so the patient was seen by dermatology. Pathology of a biopsy demonstrated ulceration with undermined borders and mixed acute and chronic lympho-histiocytic inflammatory infiltrate without evidence of malignancy or infection along with abundant dermal fibrosis suggesting a chronic process (FIG. 1). These findings were suggestive of PG, so topical tacrolimus 0.1% ointment was begun resulting in notable improvement. Systemic immunosuppression was held until the etiology of the lung lesions could be identified.

The patient underwent biopsy of the lung with chest tube placement. Lung pathology showed granulation tissue, granulomatous inflammation, and scattered giant cells without evidence of malignancy, vasculitis, or infection. A lesion clinically consistent with PG then developed at the cutaneous site of lung biopsy. Oral cyclosporine 300 mg daily was initiated and resulted in improvement but due to the development of cellulitis was discontinued. After treatment of cellulitis, he was transitioned to prednisone 80 mg by mouth daily.

Two-months later, the patient was readmitted with symptomatic anemia secondary to bleeding of bilateral lower extremity lesions (FIG. 2). This was in the context of 2 weeks of

medication noncompliance and a wound care change from silver alginate dressings to calcium alginate dressings with topical collagenase. Prednisone was restarted and collagenase was discontinued due to concern for pathergy. Topical becaplermin 0.01% gel was started on the left dorsal foot daily with significant improvement after 4 days, so application was expanded to both lower extremities. Repeat systemic vasculitis workup was negative and renal biopsy showed no evidence of glomerulonephritis. The patient improved on prednisone taper and wounds fully healed by 8 weeks post therapy (FIG. 2).

Case 2

A 40-year-old male with history of kidney transplant 7 years ago and declining renal function requiring recent initiation of hemodialysis and recent cultures positive for *E.coli* on tigecycline, presented with a two-week history of a tender ulceration on his left lower extremity. Physical examination revealed a ten by six centimeter ulceration of the left medial calf and a seven-centimeter ulceration of the left lateral leg. Adjacent to these large ulcers were dusky reticulated two to five centimeter patches with central necrosis, consistent with retiform purpura (FIG. 3). Biopsy from an area of necrosis within the retiform purpura confirmed calciphylaxis by displaying full-thickness necrosis with calcium deposition in postcapillary venules (FIG. 3).

The patient was started on IV sodium thiosulfate, five times weekly hyperbaric oxygen therapy, and topical becaplermin 0.01% gel daily beneath telfa dressings. Within 1 week, evidence of healing tissue could be found and at three weeks the ulcers displayed greater than 50% coverage with healthy granulation tissue. By week 8, the ulcers had fully granulated (FIG. 3).

Comment

PG is known to be associated with IgA paraproteinemia (3) and our patient had MGUS, IgA type diagnosed 8 years prior to pulmonary manifestations. In fact, our patient first presented with cavitary lung lesions and only later developed skin lesions consistent with PG. Standard treatment involves immune modulation and ulcers frequently take weeks to months to heal (10). Our patient also worsened greatly with topical collagenase, consistent with pathergy-induced PG.

Conversely, his skin lesions responded dramatically to topical becaplermin, a topical PDGF that is used as an adjunct treatment for diabetic foot ulcers (11). To our knowledge, there have been two reports of using becaplermin in PG (12,13). In one case associated with myelodysplastic syndrome, treatment with oral methylprednisolone and wound care with alginate and clobetasol resulted in slow healing while administration of becaplermin significantly accelerated wound closure (12). In the other case, a patient with chronic renal insufficiency and PG ulcer underwent surgical debridement and treatment with becaplermin along with meshed allografts, resulting in wound closure (13). Thus, our report adds further support to the utilization of becaplermin in PG-induced ulcers that are unresponsive to traditional therapies or need adjunctive therapies. Becaplermin can hasten wound resolution, decrease medical costs, and reduce ulcer morbidity.

Our second case used becaplermin as an adjuvant treatment for ulcers due to calciphylaxis. To our knowledge there have not been any published reports of adjunct treatment of calciphylaxis with becaplermin in the literature. In this case, becaplermin was used in addition to sodium thiosulfate and hyperbaric oxygen. Becaplermin is often used in combination with other wound healing methods such as hyperbaric oxygen, allografts, or vacuum-assisted closure (14). More trials using becaplermin for treatment of chronic wounds may show efficacy and result in its use in conditions similar to PG or calciphylaxis. Further research into the mechanism of action of becaplermin, as PGDF expression in PG and calciphylaxis is unknown, may also prove illuminating. In our two patients, becaplermin dramatically improved wound-healing time and is a therapy that can decrease medical costs and improve patient morbidity.

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FIG. 1.

Histopathology of right knee. 40 × magnification, H&E stain of edge of ulcer with underlying mixed acute and chronic inflammatory infiltrate with neutrophils and eosinophils consistent with chronic pyoderma gangrenosum. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

FIG. 2.

Pyoderma gangrenosum gross photographs. A) Location of pyoderma gangrenosum lesions on right lower leg and left dorsal foot. B) Right lower leg flaring at the beginning of the patient's last hospitalization showing a large ulcer with undermined borders and granulation tissue. C, D) Improvement in the size and extent of the ulceration over time at 3 and 7 weeks post-treatment as patient was treated with prednisone and becaplermin, with progression to pink atrophic plaques and hyperpigmented cribriform scars. E) Left dorsal foot with a large ulcer with undermined borders and crust. F, G) Resolution of left dorsal foot ulcer at 3 and 7 weeks post-treatment showing replacement with pink atrophic plaque. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

FIG. 3. Calciphylaxis gross photographs and pathology. A) Retiform purpura visible on left anterior shin as well as large ulcer of the left medial calf. B, C) Left medial calf after 3 and 8 weeks of daily therapy with 0.01% becaplermin gel. D) Histopathology of ulcer at 40 × magnification, von Kossa stain highlights calcium deposition within medium-sized vessel walls, consistent with calciphylaxis. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]