Modified dose of guselkumab for treatment of pyoderma gangrenosum

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INTRODUCTION

Pyoderma gangrenosum (PG) is an ulcerative neutrophilic dermatosis that classically affects the lower extremities. The pathophysiology of PG is incompletely understood, which makes targeted therapeutic approaches challenging. Interleukin (IL) 23, a cytokine implicated in neutrophilic diseases, has shown promise as a PG treatment target.[1] We report a case of recalcitrant PG treated with guselkumab (an IL-23 inhibitor) at a dose modified from that approved for other inflammatory conditions.

Abbreviations used:

DVT: deep venous thrombosis
IL: interleukin
LLE: left lower extremity
PG: pyoderma gangrenosum

CASE REPORT

A 49-year−old woman with well-controlled type 2 diabetes mellitus presented to urgent care with a left lower extremity (LLE) nonhealing skin ulceration following a previously sutured traumatic laceration (Fig 1, *A*). Examination revealed a 1.5 cm × 2.0 cm irregular ulcer, with undermined borders, in the subcutaneous fat. She was initially diagnosed with a vascular ulcer complicated by cellulitis and was treated with oral antibiotics; however, the ulcer continued to expand. A month later, vascular imaging identified an LLE deep venous thrombosis (DVT) and an abnormal venous reflux. Ulcer expansion after sharp debridement 3 months later increased suspicion of an inflammatory etiology.

A second LLE DVT was discovered 1 week later, prompting the initiation of rivaroxaban treatment. Subsequent ulcer biopsy findings were nonspecific, and the long-standing, refractory nature of the ulcer led to the consideration of a diagnosis of PG. This was confirmed upon referral to dermatology; the diagnosis was based on an irregular ulcer with undermined, violaceous borders, extreme pain (>4/10), and pathergy (PARACELSUS score = 10). Over the next several months, multiple systemic treatments were trialed, including cyclosporine, prednisone, and adalimumab, with variable efficacy (Fig 1, *B*). Fig 2, After the initiation of Epifix biologic dressing (MIMEDX Group, Inc.) and dapsone a year after her initial presentation, the patient was admitted for cellulitis-induced sepsis. Upon recovery, weekly Epifix, intralesional corticosteroids, prednisone, and dapsone were continued with little success. The patient was referred to tertiary care and briefly restarted on cyclosporine without improvement. Owing to continued ulcer enlargement despite multiple different treatment attempts, the decision to try off-label use of guselkumab was made.

Guselkumab was initiated at 200 mg subcutaneously, while prednisone and cyclosporine were tapered. After 2 weeks, the wound had decreased in size, and the amount of drainage had reduced. Shortly after, the patient was hospitalized a second time for *Escherichia coli* bacteremia. Following discharge and 4 weeks after the initial dose, she

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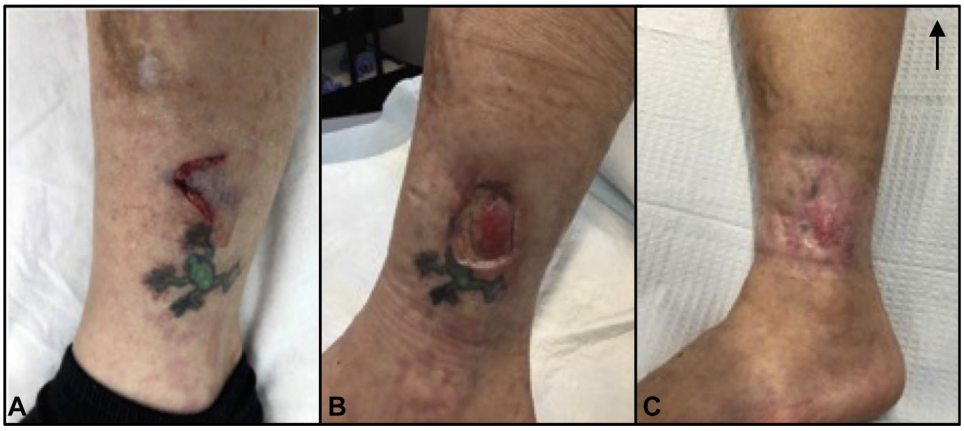

Fig 1. Pyoderma gangrenosum of the left lower extremity(LLE). **A**, LLE after injury by a dishwasher door in December 2019. **B**, LLE ulcer at initial visit with dermatology in May 2020. The lesion measured 3.5 × 4.4 cm with full-thickness ulceration and jagged, overhanging edges. **C**, Complete healing of the LLE ulcer in August 2021.

received her second guselkumab dose at 100 mg. The patient was subsequently admitted for a third instance of sepsis secondary to cellulitis and the development of a third LLE DVT, which were treated with intravenous antibiotics and continued rivaroxaban.

The patient received her third and fourth doses of guselkumab at 100 mg at 6-week intervals. She achieved complete healing after 4 doses of guselkumab (Fig 1, *C*). Fig 2, *A, B* displays the timeline of the patient's presentation, diagnosis, and treatment course. The patient had another ulcer on her right lower extremity (Fig 3, *A, B*), which healed as well (Fig 3, *C*). As of November 2021, her ulcers remain healed. The patient will continue guselkumab at 100 mg every 6 weeks for 1 year of therapy based on the authors' experience.

DISCUSSION

This case is a classic example of the diagnostic and management challenges presented by PG. As evidenced here, patients often present to nondermatologists first and undergo wound care without improvement; they may also undergo sharp debridement, further complicating their disease. The patient in this study was treated for several months before the diagnosis of PG was considered, but many others remain misdiagnosed even longer (V.E. Orfaly, BS, A.M. Reese, BS, M.A. Friedman, MD, E. Latour, MS, A.G. Ortega Loayza, MD, submitted manuscript, October 22, 2021).

PG has a misdiagnosis rate of 10% to 20%, likely due to the lack of gold standard diagnostic criteria or specific laboratory markers.[2] As was seen in 15.8% of the patients enrolled in the Pyoderma Gangrenosum Study Registry (V.E. Orfaly, BS, A.M. Reese, BS, M.A. Friedman, MD, E. Latour, MS, A.G. Ortega Loayza, MD, submitted manuscript, October 22, 2021) and in this case, patients with PG may have concurrent venous insufficiency, which further distracts from the correct diagnosis. Delayed diagnosis can have devastating consequences, including unnecessary surgical intervention, increased health care expenditures, and decreased quality of life.

Interestingly, this patient experienced multiple DVTs throughout the course of her disease, a finding also seen in 10.5% of the patients from the Pyoderma Gangrenosum Study Registry (V.E. Orfaly, BS, A.M. Reese, BS, M.A. Friedman, MD, E. Latour, MS, A.G. Ortega Loayza, MD, submitted manuscript, October 22, 2021). The development of DVTs with PG may be partially explained by the reported association between inflammation and thrombotic events, wherein inflammatory states trigger coagulation cascade activation and hypercoagulability.[3]

In addition to diagnostic challenges, no definitive treatment approach exists for PG; this is especially true for recalcitrant PG. PG treatment typically involves pain management, wound care, and targeted immunomodulation.[2] Unfortunately, without Food and Drug Administration-approved medications, coverage denial is often a barrier to appropriate immunosuppressant treatment. These therapies can lead to the development of cellulitis and bacteremia, as seen here, necessitating a delicate balance between managing infection and inflammation. With prolonged unrecognized disease, bacteria resistant to antibiotic treatment, such as *Pseudomonas aeruginosa*, may colonize.[4] The infections with gram-negative bacteria seen here may be more common in patients with PG; for instance,

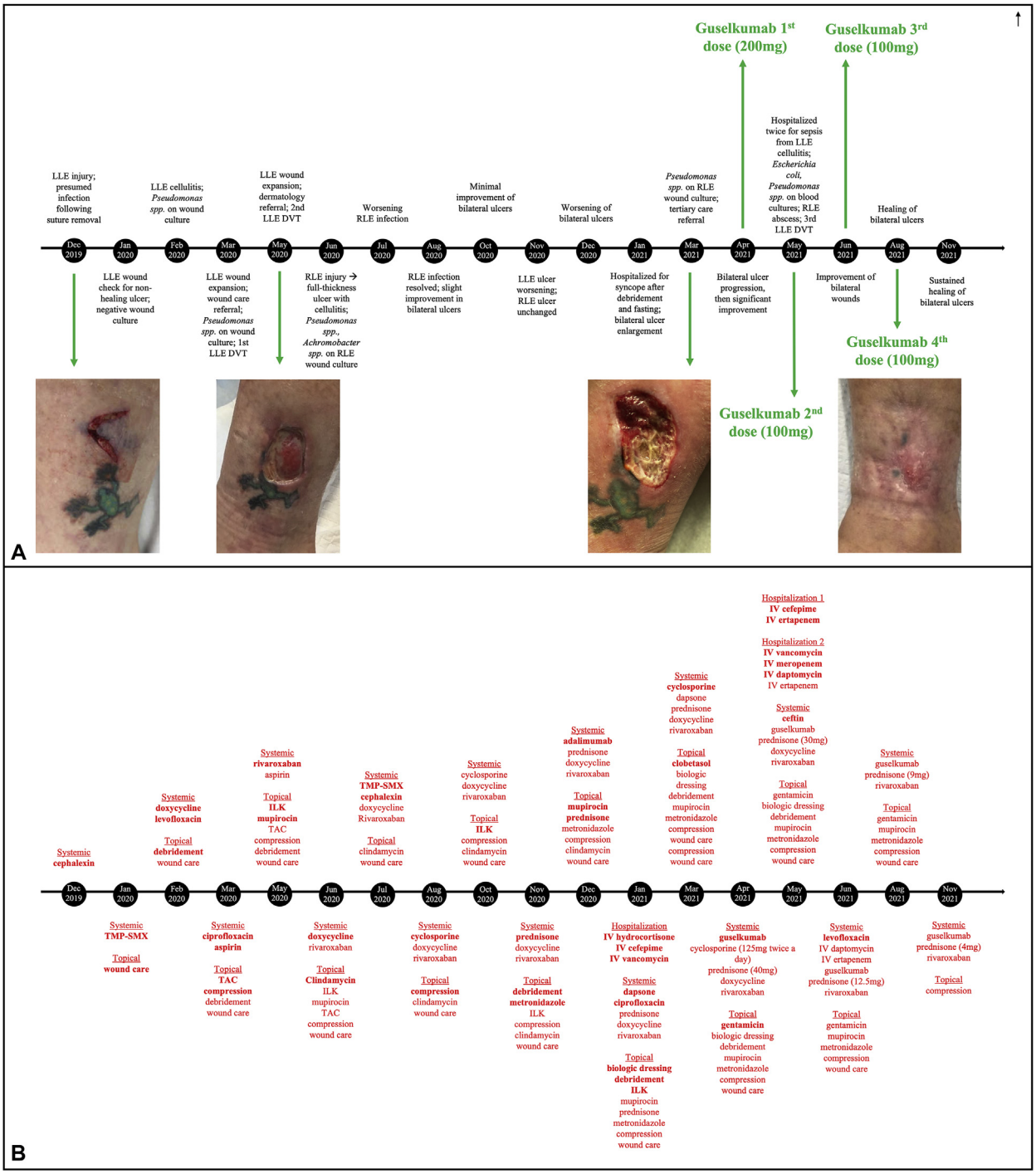

Fig 2. Timeline of presentation, diagnosis, and treatment course. **A**, Timeline from the patient's initial presentation to urgent care in December 2019 through ulcer healing in August 2021 and sustained healing as of November 2021. Images represent the left lower extremity lesion. **B**, Timeline of all the treatments utilized throughout the patient's disease course. *Bold font* indicates initiation of new treatment. *DVT,* deep venous thrombosis; *ILK,* intralesional Kenalog; *IV,* intravenous; *LLE*, Left lower extremity; *RLE,* right lower extremity; *TAC,* triamcinolone; *TMP-SMX,* trimethoprim-sulfamethoxazole.

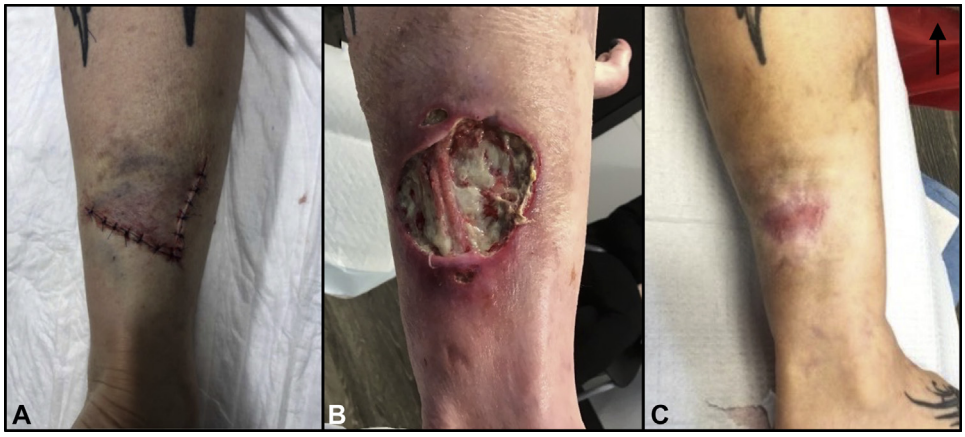

Fig 3. Pyoderma gangrenosum of the right lower extremity (RLE). **A**, RLE with sutured laceration from a mattress spring in June 2020. **B**, RLE lesion after ulceration in July 2020. The lesion was 4.4 × 3.8 cm with full-thickness ulceration, ragged undermined edges, and severe surrounding erythema. Wound cultures revealed *Pseudomonas species pluralis* spe and *Achromobacter species pluralis*. **C**, The figure shows complete healing of the RLE ulcer in August 2021.

they were observed in 29.5% of head and neck PG cases in a recent retrospective review (A.M. Reese, BS, A.S. Gupta, MD, PhD, E. Latour, MS, M. Loyo, MD, MCR, B. Kaffenberger, MD, A. Creadore, MD, A. Mostaghimi, MD, MPA, MPH, L. Seminario-Vidal, MD, PhD, J. Rick, MD, A.G. Ortega-Loayza, MD, MCR, submitted manuscript, January 19, 2022).

Biologic therapies are options for the treatment of recalcitrant ulcers. Agents targeting IL-23, such as ustekinumab and risankizumab, have recently shown promise as PG treatments. In a multicenter case series, 68% of the patients with PG ulcers refractory to multiple systemic therapies healed with ustekinumab.[5] Additionally, treatment with risankizumab resulted in significant clinical improvement in the recent reports of 2 patients with refractory PG ulcers.[6,7]

Guselkumab is another anti—IL-23 monoclonal antibody, the use of which may be beneficial in refractory PG. Its utility in PG was highlighted in a recent report of a previously recalcitrant PG ulcer that healed after 3 months of treatment with guselkumab.[8] However, this patient received guselkumab at 100 mg subcutaneously monthly for 3 months and was transitioned from ustekinumab.

This case highlights the importance of a multifaceted PG treatment approach and the many challenges in the diagnosis and management of PG. The failure of several treatment modalities leaves patients with limited alternatives. This case report supports the potential utility of modified-dose guselkumab for the treatment of refractory PG. Further studies examining the safety and efficacy of guselkumab in PG are warranted.

We would like to acknowledge the patient for her contributions to the editing of this manuscript.

We were unable to obtain consent from the tattoo artist as the patient's tattoo was over 30 years old, and she was unable to locate or contact the tattoo artist.

Conflicts of interest

Dr Ortega-Loayza has served in advisory boards for Janssen, BMS, and Boehringer Ingelheim and as a consultant for Genentech and Guidepoint. He has also received research grants from Eli Lilly Company, Oregon Health & Science University School of Medicine Gerlinger research award, and Medical Research Foundation of Oregon. Author Reese and Drs Erickson and Reed have no conflicts of interest to declare.

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