

# Pyoderma gangrenosum–like ulceration of the lower extremity secondary to sunitinib therapy: a case report

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Mildred Lopez Pineiro<sup>1</sup>, Eric Willis<sup>2</sup>, Chen Yao<sup>2</sup>  
and Susan Y Chon<sup>3</sup>

## Abstract

Sunitinib is a multi-targeted receptor tyrosine kinase inhibitor used for the treatment of multiple different types of malignancies. Serious grade 3–4 adverse events occur in <10% of the patient population and usually improve with dose reduction. One of the more rarely reported side effects of sunitinib therapy is the development of pyoderma gangrenosum–like ulcerations in the lower extremities. These pyoderma gangrenosum–like ulcerations are difficult to treat and distinguish from similar-appearing dermatological diagnoses. We present a patient with refractory lung carcinoma and a past medical history of squamous cell carcinoma of the lower extremity, who developed a non-healing ulceration at the previous site of her skin cancer while undergoing therapy with sunitinib. At the time of the initial evaluation, the ulceration mimicked recurrent squamous cell carcinoma, posing a diagnostic challenge. Histopathological findings showed epidermal hyperplasia, ulceration, and dense acute inflammation. Despite meticulous wound care and treatment of infection, the ulcer only improved with cessation of sunitinib.

## Keywords

Lower extremity ulcer, pyoderma gangrenosum, sunitinib adverse effect

## Introduction

Pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis that presents as a painful, necrotic ulceration. It typically affects patients in the third to sixth decades of life, occurring most frequently on the lower extremities. Histologically, PG is a diagnosis of exclusion and has to be distinguished from other causes of ulceration such as infection, cutaneous malignancies, or vascular disease. Pathogenesis of PG is still currently unknown, but possible theories include occult bacterial infection, autoantibodies, and the Shwartzman reaction, which is a local immune response to bacterial endotoxin resulting in tissue necrosis. Management of PG typically requires multiple modalities to reduce inflammation and optimize wound healing, in addition to treatment of any underlying disease.<sup>1</sup> Prednisone and cyclosporine have been mainstays of systemic treatment for PG, although increasing evidence supports the use of biological therapies, such as tumor necrosis factor- $\alpha$  inhibitors, for refractory cases of PG.<sup>2</sup>

Sunitinib is a multikinase inhibitor that targets the platelet-derived growth factor (PDGF)- $\alpha$ , PDGF- $\beta$ , vascular endothelial growth factor receptor (VEGFR)-1–3, c-Kit,

FMS-like tyrosine kinase-3 (FLT3), colony stimulating factor 1 (CSF-1), and rearranged during transfection (RET) receptor that is typically used in the treatment of renal cell carcinoma, hepatocellular carcinoma, and gastrointestinal stromal tumors.<sup>3–5</sup> PG-like ulcerations due to sunitinib have been suggested to be due to the antiangiogenic effects of sunitinib by c-Kit and VEGFR inhibition that induce necrosis and subsequent invasion of neutrophilic granulocytes causing this neutrophilic dermatosis (Figure 1). The mainstay of therapy for severe adverse drug reactions is

<sup>1</sup>Department of Dermatology, University of Texas McGovern Medical School at Houston, Houston, TX, USA

<sup>2</sup>University of Texas McGovern Medical School at Houston, Houston, TX, USA

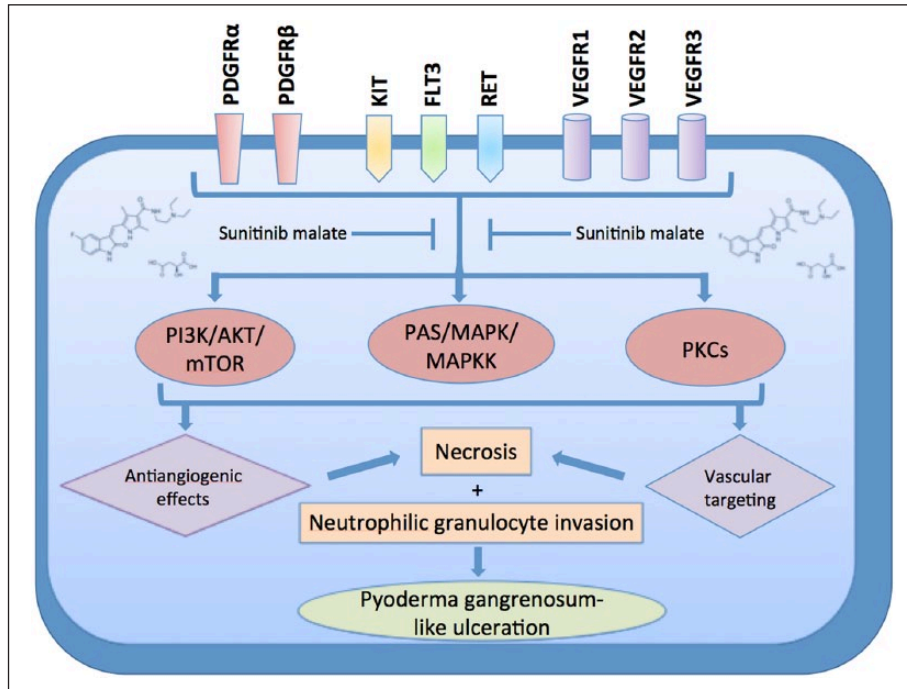
<sup>3</sup>Department of Dermatology, University of Texas MD Anderson Cancer Center, Houston, TX, USA

## Corresponding Author:

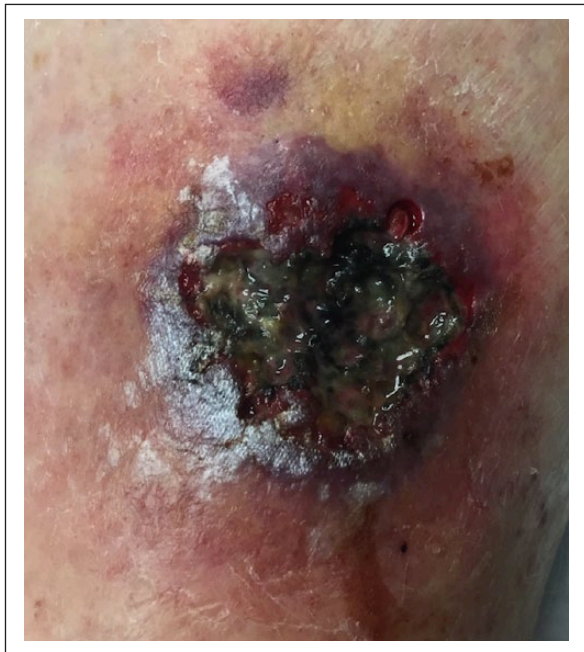
Mildred Lopez Pineiro, Department of Dermatology, University of Texas McGovern Medical School at Houston, 6655 Travis Street, #700, Houston, TX 77030, USA.

Email: Mildred.LopezPineiro@uth.tmc.edu

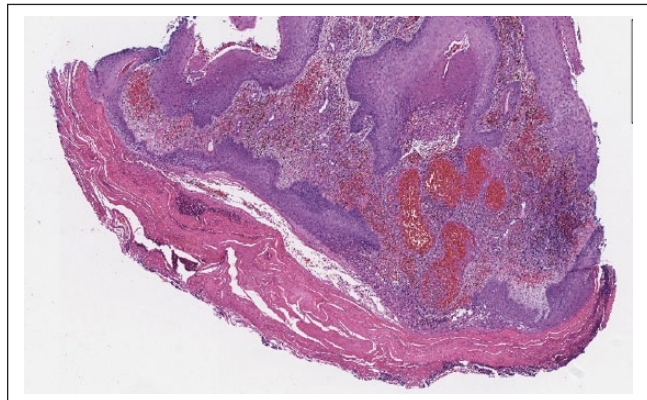




**Figure 1.** Sunitinib mechanism of action in inducing pyoderma gangrenosum involves the inhibition of c-Kit and VEGFR.



**Figure 2.** A 2.9 cm × 1.8 cm ulcer with beefy red edges and an overlying black eschar, draining serosanguinous fluid without gross purulence.

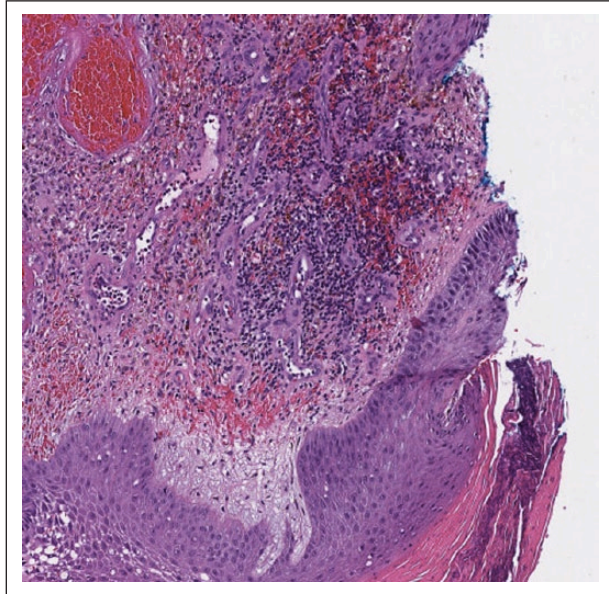


**Figure 3.** Epidermal hyperplasia, ulceration, and dense acute inflammation with neutrophils and crusting shown at 10×.

### Case presentation

We present the case of a 73-year-old female with a history of lung carcinoid tumor as well as squamous cell skin cancers who presented to our clinic for evaluation and management of a non-healing ulcer on the left lower extremity. Initial biopsy showed a squamous cell carcinoma in situ and she was treated with electrodesiccation and curettage. One year later, after having failed multiple chemotherapeutic and targeted agents for treatment of lung carcinoid tumor, she was started on sunitinib in combination with lanreotide and was doing well. Another year passed and the patient presented to our clinic with concerns for recurrence of the squamous cell

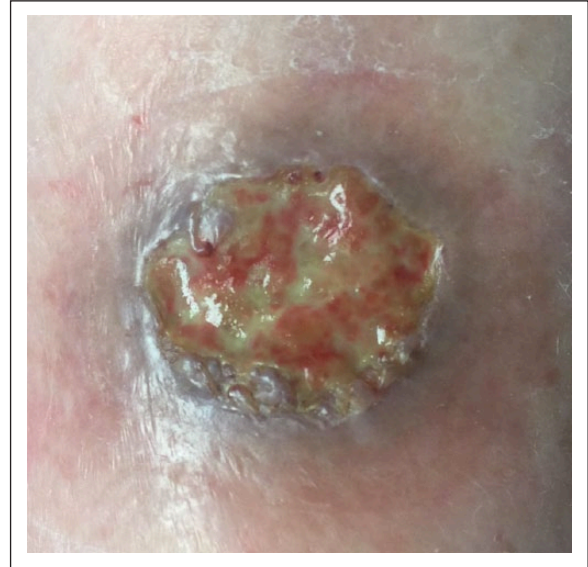
discontinuation of the suspected medication.<sup>5,6</sup> Systemic corticosteroids and immunosuppressive agents can accelerate the healing time, but are not curative if the causative drug is continued.



**Figure 4.** Close-up on dense acute inflammation with neutrophils and red blood cell extravasation shown at 20 $\times$ .

carcinoma in situ of the left lower leg as she had again a non-healing ulceration. This ulcer was biopsied two times showing scar and pigmented macrophages. Wound culture grew *Serratia marcescens* and *Corynebacterium*. However, the skin failed to improve with conventional therapies including oral antibiotics including Bactrim and doxycycline, topical antibiotics including mupirocin and silver sulfadiazine, and regular alginate dressing changes. Sunitinib was stopped with the idea that this medication could have been preventing wound healing. The ulcer improved with almost complete resolution, and sunitinib was restarted. She presented again for follow-up examination at which time she had a recurrent 2.9 cm  $\times$  1.8 cm ulcer with beefy red edges and an overlying black eschar, draining serosanguinous fluid without gross purulence (Figure 2). A third skin biopsy was then performed and showed epidermal hyperplasia, ulceration, and dense acute inflammation with neutrophils and crusting (Figures 3 and 4). Methenamine silver, Fite stain, acid-fast bacilli (AFB), and periodic acid Schiff (PAS) were negative. There was no malignancy identified. Imaging ruled out bone involvement. The patient was restarted on oral antibiotic doxycycline. Due to concerns for drug-induced PG as reported in the literature, sunitinib was stopped. The ulceration improved and she was taken off of antibiotics. She had almost complete resolution of the ulcer (Figure 5).

Drug-induced PG is a rare but serious adverse drug reaction that has been reported in the literature. Clinicians should have a high level of suspicion when caring for the skin of oncologic patients undergoing this therapy, as a change in their treatment plan can lead to resolution of this adverse cutaneous drug reaction.



**Figure 5.** Almost complete resolution of the ulcer with healthy granulation tissue.

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#### Informed consent

Informed consent for patient information and images to be published was obtained.

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