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Leflunomide-induced and paraneoplastic ulcers in a rheumatoid arthritis patient



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Key words: large granular lymphocytic leukemia; leflunomide; paraneoplastic; pyoderma gangrenosum; rheumatoid arthritis; ulcer.

INTRODUCTION

Patients with rheumatoid arthritis (RA) are predisposed to ulcer formation because of their primary disease process, treatment regimens, and comorbid conditions.¹ Recently, ulceration in RA patients has been linked to both an RA treatment (leflunomide)²⁻⁵ and a rare malignancy associated with RA (large granular lymphocytic [LGL] leukemia).⁶

We present a patient with RA who developed leflunomide-induced cutaneous ulceration (LICU) after 10 years of treatment. Additionally, we explored the possible relationship of LGL leukemia and neutropenia that may have produced pyoderma-gangrenosum-like lesions 8 months after this patient's initial LICU presentation.

CASE REPORT

A 68-year-old female with RA managed on leflunomide 20 mg daily for 12 years presented in August 2019 with a 2-year history of recurrent, slowly-healing, painful mucosal, and cutaneous ulcers. She had previously been evaluated for "sores" on the buccal mucosa, lip, elbow, and mons pubis that each resolved within 6 weeks of appearance (Supplementary Table I, available via Mendeley at <https://doi.org/10.17632/v7hv6js882.1>). When she presented to our clinic, her lesions had been present for several months. Physical examination revealed 2 ulcers with central eschar and surrounding erythema (Fig 1, A: 1.5 cm ulcer of the left medial calf; 0.4 cm ulcer of the right posterior leg); a 0.2 cm left helix ulcer with minimal erythema;

Abbreviations used:

LICU:	Leflunomide-Induced Cutaneous Ulceration
LGL:	Large Granular Lymphocytic
PG:	Pyoderma Gangrenosum
RA:	Rheumatoid Arthritis

and a 0.3 mm left, lateral tongue erosion. Biopsy demonstrated dermal vascular changes with fibrosis, fat necrosis, and mixed inflammation, and tissue cultures resulted in no growth (Supplementary Table D). Laboratory workup to evaluate the patient for vasculitis/vasculopathy revealed depressed C4, elevated C-reactive protein and rheumatoid factor, positive anti-nuclear antibody, mild thrombocytopenia, and resolving neutropenia (Supplementary Table II, available via Mendeley at <https://doi.org/10.17632/v7hv6js882.1>).

This patient's clinical course is summarized in Fig 1. Following a diagnosis of LICU, leflunomide was discontinued, a 14-day cholestyramine washout regimen was initiated based on prior LICU reports,^{5,7} and anti-inflammatory medications were prescribed (clobetasol ointment, doxycycline). Initially, the patient's ulcers expanded; a new right ankle ulcer appeared; and 2 left lower extremity deep venous thromboses were identified and treated with apixaban. In November 2019, LICU inflammation was noted to have resolved, and so irrigation, debridement, and split-thickness skin grafting of the leg wounds were performed. The right leg wound

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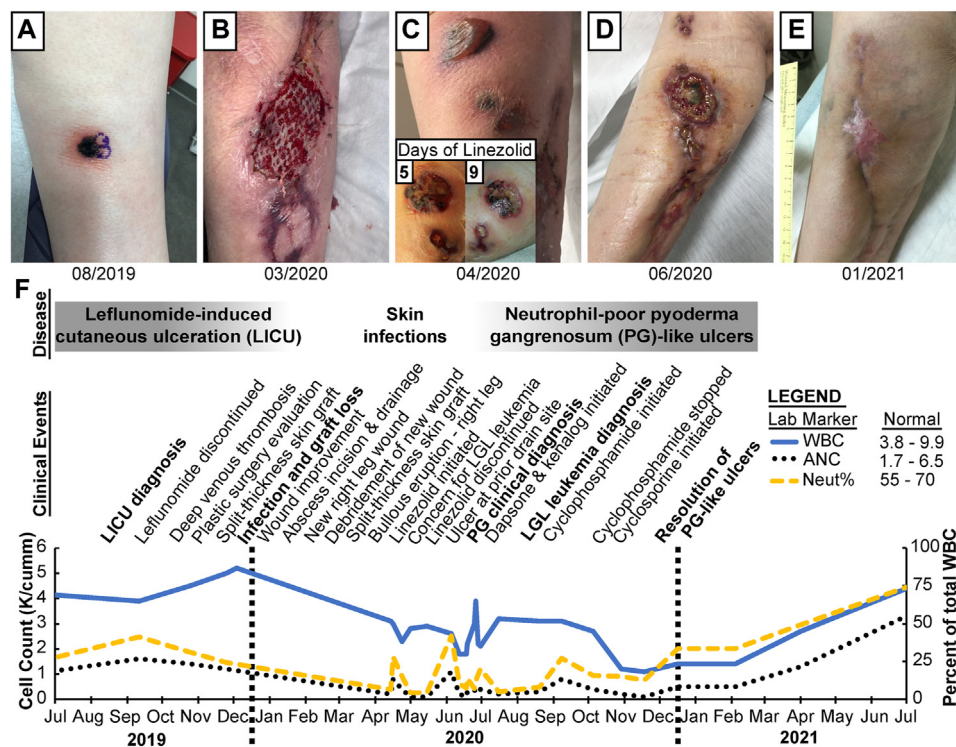


Fig 1. Leflunomide-induced cutaneous ulceration and pyoderma gangrenosum-like ulcer images and clinical course timeline. **A**, Leflunomide-induced cutaneous ulceration on left medial calf at initial presentation with punch biopsy sites marked. **B**, Right calf following repeat split-thickness skin graft. **C**, Bullous *Corynebacterium striatum* eruption (1 intact bulla and 2 ruptured bullae) on right lower extremity is shown with inset images of clinical improvement following 5 and 9 days of linezolid treatment. **D**, Ulcers concerning for neutrophil-poor pyoderma gangrenosum on right lower extremity. **E**, Healed ulcer site on right calf. **A-E**, Image dates are listed below each image. **F**, The clinical course for the patient’s lower extremity disease is outlined above complete blood count monitoring (left vertical axis: white blood cell [WBC] and absolute neutrophil count [ANC], right vertical axis: neutrophil percentage, horizontal axis: time). ANC, Absolute neutrophil count; LICU, leflunomide-induced cutaneous ulceration; Neut%, neutrophil percentage; PG, pyoderma gangrenosum; WBC, white blood cell.

healing was complicated by infections from December 2019 to March 2020 (Supplementary Tables I and III, available via Mendeley at <https://doi.org/10.17632/v7hv6js882.1>; Fig 1, F) that led to near-complete graft loss and incision, and drainage for an abscess. In April 2020, a repeat skin graft was performed (Fig 1, B), which was complicated by a bullous *Corynebacterium striatum* infection (Fig 1, C; Supplementary Tables I and III). Linezolid treatment of the *C. striatum* infection led to decreased peripheral erythema and the appearance of granulation tissue within fibrinous wound beds.

Laboratory monitoring for linezolid therapy revealed anemia and neutropenia (Supplementary Table II). A recent chest CT (12/2019) had not shown hepatosplenomegaly. A leukemia workup was initiated. Peripheral blood flow cytometry showed lymphocytosis with circulating LGLs with an

abnormal CD4-positive, CD7-negative T-cell population. Clonal T-cell receptor gamma gene rearrangement was also detected.

In June 2020, the 3 previous *C. striatum* bullae were unroofed but not healed, and 2 new ulcers had developed at a prior surgical drain site (Fig 1, D). These 5 ulcers were noted to have violaceous, undermined borders. Multiple skin biopsies showed no evidence of microorganisms and paired tissue culture demonstrated no growth (Supplementary Table I), which in the setting of neutropenia led to a clinical diagnosis of neutrophil-poor pyoderma gangrenosum (PG). Oral dapsone and intralesional triamcinolone to PG borders were started, and the patient was referred to our institution’s wound clinic. A bone marrow biopsy in August 2020 revealed granulocytic hyperplasia and lymphocytic infiltrate, which led to a diagnosis of LGL leukemia. Following

cyclophosphamide induction, our patient was maintained on cyclosporine, dapsone, and intralesional triamcinolone. By January 2021, all cutaneous lesions had healed with some “cigarette paper-like” scarring (Fig 1, E). Six months later, dapsone was tapered over 2 months. Five months after cessation of dapsone, the patient was still free of PG-like ulcers with well-controlled LGL on cyclosporine 50 mg daily.

DISCUSSION

Our patient presented with LICU in August 2019 and then was clinically diagnosed with pyoderma gangrenosum in June 2020 in the setting of LGL leukemia and neutropenia. LICU is a recently recognized rare effect of leflunomide use.²⁻⁵ A probable causal relationship between leflunomide and our patient's initial cutaneous ulceration was demonstrated through application of the Naranjo probability scale (Supplementary Table IV, available via Mendeley at <https://doi.org/10.17632/v7hv6js882.1>).⁸ Ulcer resolution following leflunomide discontinuation and cholestyramine washout was comparable to previous reports.^{5,7}

This report differs from previous accounts of LICU where ulcers appeared within 4-12 months of leflunomide initiation.²⁻⁵ Our patient took leflunomide daily for 10 years before developing ulcers. This suggests prior tolerance of leflunomide may not confer future protection from LICU. However, the cause of ulceration may be multi-factorial and this patient's hematologic abnormalities likely played a role in lesion formation (eg, poor wound healing due to impaired neutrophil maturation/function, impaired T cell activity due to LGL leukemia).

The lesions in June 2020 were clinically diagnosed as PG. Strict application of the 2018 Delphi consensus criteria did not support a diagnosis of PG in this patient (Supplementary Table V, available via Mendeley at <https://doi.org/10.17632/v7hv6js882.1>), but the application of the 2018 PARACELUS criteria did support the diagnosis of PG in this patient (Supplementary Table VI, available via Mendeley at <https://doi.org/10.17632/v7hv6js882.1>).⁹ Due to this inconsistency, we refer to this patient's ulcers in June 2020 as PG-like.

Recently, Koechel et al⁶ reported PG-like ulcers in a T-cell LGL leukemia patient. Their biopsy demonstrated a neutrophil-rich infiltrate. We hypothesize that our patient's LGL leukemia compromised neutrophil maturation and function leading to neutropenia and neutrophil-poor, PG-like lesions. Further, we propose that treatment of her LGL leukemia helped normalize neutrophil maturation and T-cell activity leading to the resolution of her PG-like lesions.

Patients with RA are prone to cutaneous ulceration for many reasons. In our patient, we favor that leflunomide and LGL leukemia contributed to the formation of her cutaneous ulcerations. Due to the overlap of these etiologies, we recommend that medical providers consider workup for LGL leukemia when an RA patient presents with ulcers concerning for LICU.

Conflicts of interest

None disclosed.

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