CASE REPORT

Leflunomide-induced and paraneoplastic ulcers in a rheumatoid arthritis patient

Michael R. Vittori, MD, PharmD,a Jonathan Z. Tang, BA,b and William H. McCoy IV, MD, PhDc

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; 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 I). 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

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

From the Department of Internal Medicine; Brown University, Providence, Rhode Island; Department of Medicine, Washington University School of Medicine, St. Louis, Missouri; and Division of Dermatology, Department of Medicine, Washington University School of Medicine, St. Louis, Missouri.

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Correspondence to: William H. McCoy, IV, MD, PhD, Division of Dermatology, Department of Medicine, Washington University

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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
Recently, Koechel et al.\(^6\) 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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