Ulcerative necrobiosis lipoidica in the setting of anti–tumor necrosis factor-α and hydroxychloroquine treatment for rheumatoid arthritis

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INTRODUCTION

Necrobiosis lipoidica (NL) is a rare, chronic granulomatous disease that affects the dermis with collagen degeneration.[1] It can be associated with several conditions including diabetes mellitus, sarcoidosis, rheumatoid arthritis (RA), inflammatory bowel disease, autoimmune thyroiditis, and monoclonal gammopathy.[1,2] NL typically develops in the third to fourth decade of life with a slight female predominance.[1] In about one-third of cases, ulceration can develop as a complication, which poses unique treatment challenges to providers, as it is often recalcitrant to treatment.[2,3] The literature suggests that anti–tumor necrosis factor-α medications represent a promising therapeutic strategy for ulcerative disease.[3,4] Here we present a case of ulcerative NL that developed in the setting of etanercept and hydroxychloroquine treatment, and subsequently re-epithelialized with aggressive local treatment and discontinuation of etanercept.

Abbreviations used:

NL: necrobiosis lipoidica
RA: rheumatoid arthritis

CASE REPORT

A 44-year-old white woman with a nearly 20-year history of seropositive RA presented with an 8-month history of right lower leg ulceration with associated pain and drainage. She was managed by the rheumatology department, and was on a stable regimen of hydroxychloroquine 200 mg twice daily, diclofenac 50 mg 3 times daily, and a 15-year history of weekly etanercept 50-mg subcutaneous injections. Before her initial presentation, she had undergone a workup by her primary care physician and a vascular surgeon and was ultimately given a diagnosis of venous stasis. She had also completed a 2-week trial of Unna boot therapy and had an outside biopsy completed that was consistent with fibrosis and scar tissue.

Initial examination found a 3.0- x 2.4-cm pink, firm sclerotic plaque proximal to the right lateral malleolus with multiple small ulcerations and a deeper central 4-mm ulceration with associated purulent discharge. Motor, sensory, and circulatory examination findings were within normal limits. A bacterial culture completed at the time of her first visit showed heavy growth of group B streptococcus, for which she was treated with a 2-week course of cephalexin. After resolution of this secondary infection, examination at her follow-up visit 2 weeks later found a firm erythematous plaque with multiple clean ulcerations tracking deep into the dermis, prompting a punch biopsy for further workup (Fig 1).

Histologic examination of her biopsy specimen found a granulomatous inflammatory infiltrate with histiocytes in the interstitium arranged in layered palisades extending from the superficial portions of the biopsy to the deeper layers of the reticular dermis. Foci of degenerated collagen were present

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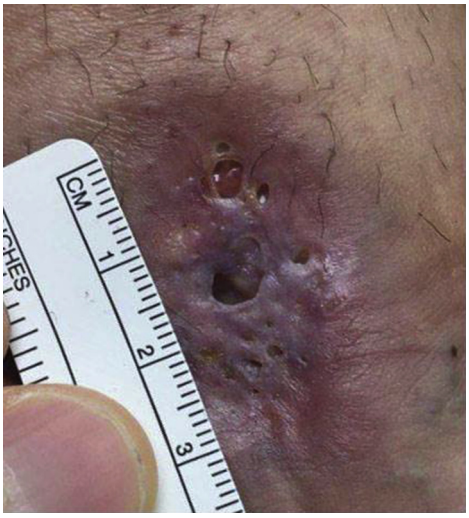

Fig 1. Clinical examination at time of biopsy. A 3.0-cm firm erythematous plaque with multiple clean ulcerations tracking deep into the dermis of right lower leg, proximal to medial malleolus.

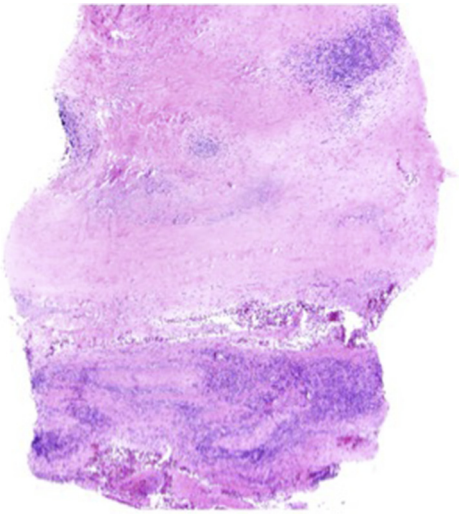

Fig 2. Representative section of the patient's punch biopsy shows a granulomatous inflammatory infiltrate, with histiocytes in the interstitium arranged in layered palisades, involving the deeper aspects of the reticular dermis. Foci of degenerated collagen are present among the layered palisades, and the infiltrate contains numerous plasma cells. Acid-fast bacillus and Gomori methenamine-silver stains were negative. (Hematoxylin-eosin stain; original magnification: ×40.)

among the layered palisades, and the infiltrate was also noted to contain numerous plasma cells. Infectious stains were negative for micro-organisms (Fig 2). These histologic findings were consistent with a diagnosis of NL.

Initial management of this ulcerative NL in the setting of systemic therapy for RA included a 3-week oral prednisone taper, pentoxifylline 400 mg 3 times daily, and topical tacrolimus 0.1% ointment twice daily to the ulcerated areas. She also began follow-up every 3 weeks, receiving local intralesional injections of triamcinolone to the inflamed periphery of the ulcer at each visit. She showed consistent clinical improvement with this aggressive local treatment regimen. The ulcer completely re-epithelialized after 19 weeks. At her most recent visit, approximately 38 weeks after diagnosis, she was noted to not only have completely re-epithelialized but showed minimal erythema or induration with only localized atrophy (Fig 3). Incidentally, after approximately 2 to 3 months of the above aggressive local treatment, the patient stopped both her weekly etanercept injections and hydroxychloroquine for 3 months because of no scheduled follow-up with her rheumatologist. She continues to follow up regularly in the clinic and is reluctant to resume these systemic medications for her RA given the improvement in healing of her ulcerative NL and minimal arthritis symptoms.

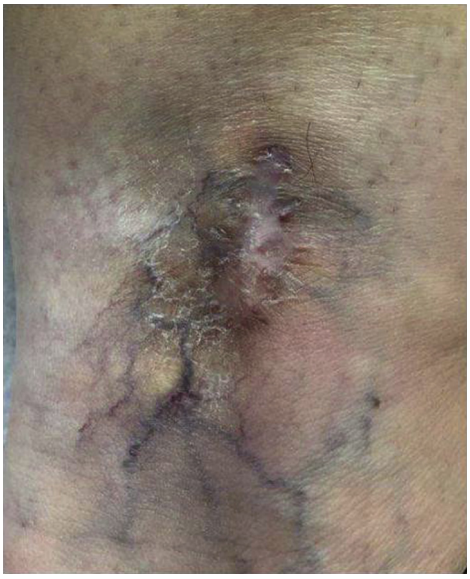

Fig 3. Clinical examination at time of most recent follow-up. Atrophic pink plaque with prominent telangiectatic blood vessels throughout. No residual ulcerations.

DISCUSSION

There are a multitude of possible treatment options for NL. A single treatment of choice is lacking, likely because of limited or incomplete knowledge regarding the pathophysiology of this disease process. Treatments can be organized into several categories including topical therapy, local therapy, systemic therapy, surgical treatments, and physical modalities (Fig 4).[1,2]

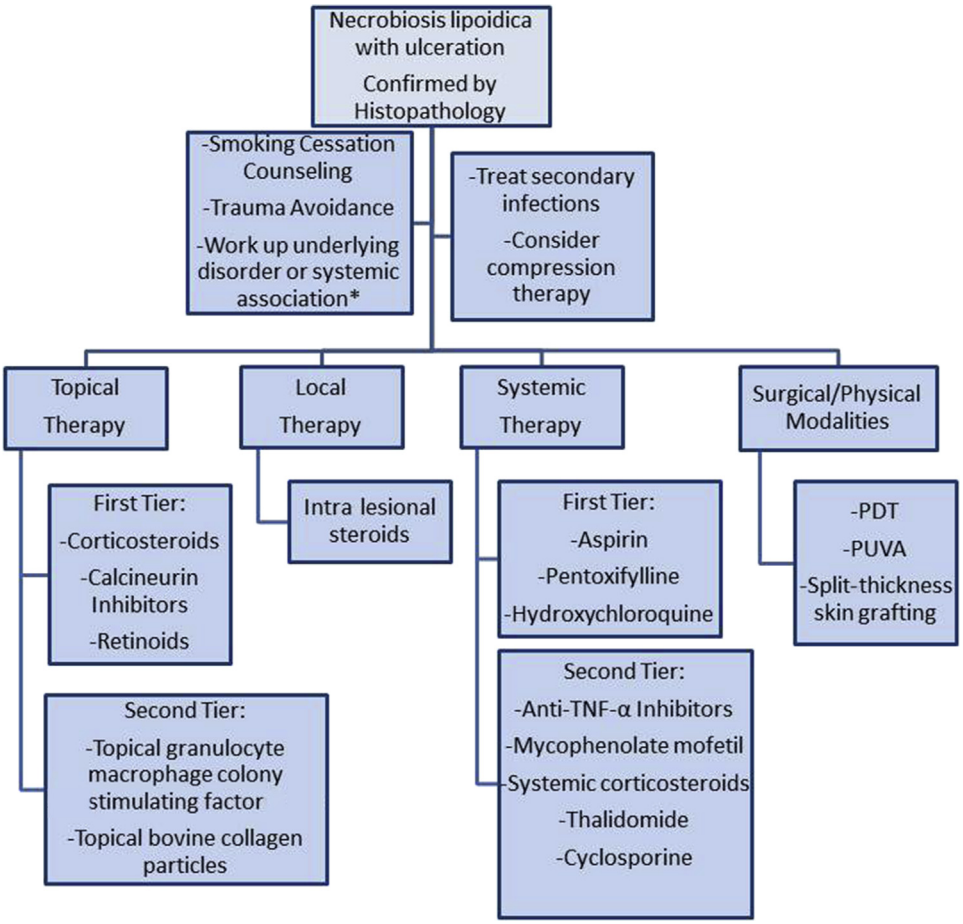

Fig 4. Treatment algorithm designed for the patient. As the patient presented on hydroxychloroquine and etanercept, she was started on topical and local treatments. In addition another first-tier systemic medication, pentoxifylline was added to her regimen. Asterisk represents complete full review of symptoms. Consider blood testing including fasting blood glucose, Hemoglobin A1c, thyroid-stimulating hormone/T4, rheumatoid factor, serum protein electrophoresis/urine protein electrophoresis, and angiotensin converting enzyme inhibitor level. *PDT*, Photodynamic therapy; *PUVA*, psoralen ultraviolet A; *TNF*, tumor necrosis factor. Adapted from Sibbald and Alavi.[2]

Ulcerative NL represents a therapeutic challenge, as it is notoriously recalcitrant to treatment. Medications most commonly seen and discussed in the literature include topical calcineurin inhibitors, pentoxifylline, etanercept, adalimumab, and infliximab.[3-8] Our patient presented with ulcerative NL despite her systemic treatment for RA, which included 2 of the recommended treatment options for NL: hydroxychloroquine and etanercept. To date, one case report describes similar concurrent development of NL in a patient with RA on a combination of methotrexate, adalimumab, and prednisone.[9] This patient did not have the complication of ulceration and was treated with topical clobetasol and intralesional triamcinolone with modest improvement noted.[9] It has been argued that etanercept may have greater efficacy than adalimumab for the treatment of NL, as a few case reports document improved clinical response after switching medications.[9,10] Our patient represents a unique case given that she had progressive ulcerative disease while on weekly etanercept injections, suggesting that NL does not show consistent clinical response to etanercept.

For our patient, we proposed a reverse treatment algorithm adapted from the approach outlined by Sibbald and Alavi.[2] Because she presented to us on both first- and second-tier systemic medications, we started both topical and local corticosteroid therapy as well as adding additional first- and second-tier systemic treatment with pentoxifylline and prednisone. During her aggressive local treatment, but without the direction of her rheumatologist, she also discontinued her systemic medications for RA.

To our knowledge, this represents the first reported case of ulcerative NL developing in the setting of etanercept therapy. This finding argues against the greater efficacy of etanercept previously discussed in the literature, although the results described should not be generalized without further study. Her clinical improvement in the setting of etanercept discontinuation could also indicate a paradoxical response to the anti—tumor necrosis factor-α inhibitors that may play a role in the pathophysiology of this disease process. However, this is slightly less likely given the many years she was on etanercept without NL development. Further studies elucidating the pathophysiology of NL are necessary to investigate this hypothesis and streamline treatment recommendations.

REFERENCES

1. Reid SD, Ladizinski B, Lee K, Baibergenova A, Alavi A. Update on necrobiosis lipoidica: A review of etiology, diagnosis, and treatment options. *J Am Acad Dermatol*. 2013;69(5):783-791.
2. Sibbald C, Reid S, Alavi A. Necrobiosis lipoidica. *Dermatol Clin*. 2015;33:343-360.
3. Basoulis D, Fragiadaki K, Tentolouris N, Sfikakis PP, Kokkinos A. Anti-TNF α treatment for recalcitrant ulcerative necrobiosis lipoidica diabeticorum: A case report and review of the literature. *Metabolism*. 2016:569-575.
4. Suarez-Amor O, Perez-Bustillo A, Ruiz-Gonzalez I, Rodriguez-Prieto MA. Necrobiosis lipoidica therapy with biologicals: an ulcerated case responding to etanercept and a review of the literature. *Dermatology*. 2010;221:117-121.
5. Kavala M, Sudogan S, Zindanci I, et al. Significant improvement in ulcerative necrobiosis lipoidica with hydroxychloroquine. *Int J Dermatol*. 2010;49:466-474.
6. Hu S, Bevona C, Winterfield L, Qureshi A, Li V. Treatment of refractory ulcerative necrobiosis lipoidica diabeticorum with infliximab: report of a case. *Arch Dermatol*. 2009;145(4):437-439.
7. Wee E, Kelly R. Pentoxifylline: An effective therapy for necrobiosis lipoidica. *Australas J Dermatol*. 2017;58:65-68.
8. Shah SD, Kale GV. Treatment of refractory ulcerative necrobiosis lipoidica diabeticorum with oral thalidomide. *Indian Dermatol Online J*. 2016;7(1):43-45.
9. Chung CG, Rosengrant A, Helm KF, Shupp DL. Necrobiosis Lipoidica occurring in a patient with rheumatoid arthritis on concurrent tumor necrosis factor-α inhibitor therapy. *Int J Dermatol*. 2015;54:1294-1296.
10. Zhang KS, Quan LT, Hsu S. Treatment of necrobiosis lipoidica with etanercept and adalimumab. *Dermatol Online J*. 2009;15(12):12.