Treatment-resistant ulcerative necrobiosis lipoidica in a diabetic patient responsive to ustekinumab

Aunna Pourang[1] MD, Raja K Sivamani[1-3] MD MS AP

Affiliations: [1]Department of Dermatology, University of California, Davis, Sacramento, California, USA, [2]Department of Biological Sciences, Davis, California, USA, [3]California State University, Sacramento, California, USA

Corresponding Author: Raja Sivamani MD, MS, CAT, Department of Dermatology, University of California, Davis, 3301 C Street, Suite 1400, Sacramento, CA 95816, Tel: 916-703-5145, Fax: 916-734-7183, Email: raja.sivamani.md@gmail.com

Abstract

Necrobiosis lipoidica is a chronic granulomatous disease of unknown etiopathogenesis, which is often difficult to treat. While data from randomized controlled trials for the treatment of necrobiosis lipoidica is lacking, several treatments of varying efficacy for necrobiosis lipoidica have been reported in the scientific literature. We present a case of a 29-year-old female with uncontrolled diabetes and treatment-resistant necrobiosis lipoidica which was responsive to ustekinumab.

Keywords: necrobiosis lipoidica, ustekinumab, granulomatous dermatitis, Th1, macrophage, IFNγ

Introduction

Necrobiosis lipoidica is a rare, chronic, cutaneous granulomatous disease that primarily affects young and middle-aged adults, with an increased predilection for females [1, 2]. It is often associated with diabetes mellitus and was called "necrobiosis lipoidica diabeticorum" in the past. This terminology was later changed to necrobiosis lipoidica and occurs in the absence of diabetes mellitus, although it is worth noting that necrobiosis lipoidica may precede a diagnosis of diabetes mellitus and occurs in about 0.3-1.2 percent of individuals with diabetes mellitus [1, 3, 4]. An association of necrobiosis lipoidica with other systemic diseases such as thyroiditis, inflammatory bowel disease, sarcoidosis, obesity, and cardiovascular disease has also been found and squamous cell cancer can occur in necrobiosis lipoidica lesions [5-7]. The pathogenesis of necrobiosis lipoidica is unclear but multiple theories exist, including impaired neutrophil migration, collagen defects, immunoglobulin deposition, and microangiopathy secondary to blood vessel glycoprotein deposition [1, 8-12]. Lesions often initially present as asymptomatic papules and nodules and over time, evolve into well-demarcated yellow brown plaques with violaceous borders, central waxy atrophic appearance, and telangiectasias [13]. Lesions can ulcerate and become painful in some individuals and koebnerization can also occur [1, 2, 14-16]. Although the pretibial area is most often commonly affected, necrobiosis lipoidica can occur on other parts of the body as well [13]. Histological findings typically show a diffuse palisaded and interstitial granulomatous dermatitis with focal connective tissue degeneration and vascular changes, but the appearance can vary throughout the course of the disease and among different patients [1, 17]. Treatment of necrobiosis lipoidica is often challenging and when lesions do resolve, post-inflammatory and atrophic changes can still persist [13]. The quality of life of individuals with this disease is significantly affected as a result of its recalcitrant nature.

Case Synopsis

A 29-year-old woman with a history of poorly controlled diabetes, depression, hypertension, and a one pack-per-day smoking history presented on initial consultation to our dermatology clinic with painful skin lesions on her lower legs that had started off as a small spot on her left shin four years prior. Since the initial lesion she progressively developed more and larger plaques on both lower legs, which

would ulcerate, bleed, and drain pus **(Figure 1A, B)**. She had been diagnosed with necrobiosis lipoidica based on a biopsy done by an outside dermatology office a few months prior. Her previous treatment course included multiple topical, systemic, and intralesional steroids, topical tacrolimus, oral antibiotics and antifungals, and hydroxychloroquine, which had been unsuccessful at resolving the lesions. For several months after presentation to our office, the patient's treatment plan included many different medications including an increase in hydroxychloroquine, as well as topical clobetasol occlusion wraps. Phototherapy was deferred owing to distance of travel for the patient. Pentoxifylline was started but discontinued after the patient reported gastrointestinal side effects. Adalimumab was initiated but then discontinued because of the development of an abdominal rash and urticarial plaques at the injection site. The patient also continued to develop new plaques despite treatment with pentoxifylline and adalimumab. Intralesional triamcinolone injections provided partial improvement, but her condition was complicated by several pseudomonal bacterial infections, requiring several courses of antibiotics. Given minimal response to the aforementioned treatments, ustekinumab was initiated in addition to the continuation of hydroxyquinone and topical clabetasol occlusion wraps. The ustekinumab was dosed at 90mg every two months as this was successful in another patient [18]. After a few months of therapy with ustekinumab, the patient's skin lesions improved, despite being hospitalized once for cellulitis **(Figure 1C, D)**. It was decided that with any future intralesional triamcinolone injections she would be dosed prophylactically with antibiotics to prevent secondary bacterial infections.

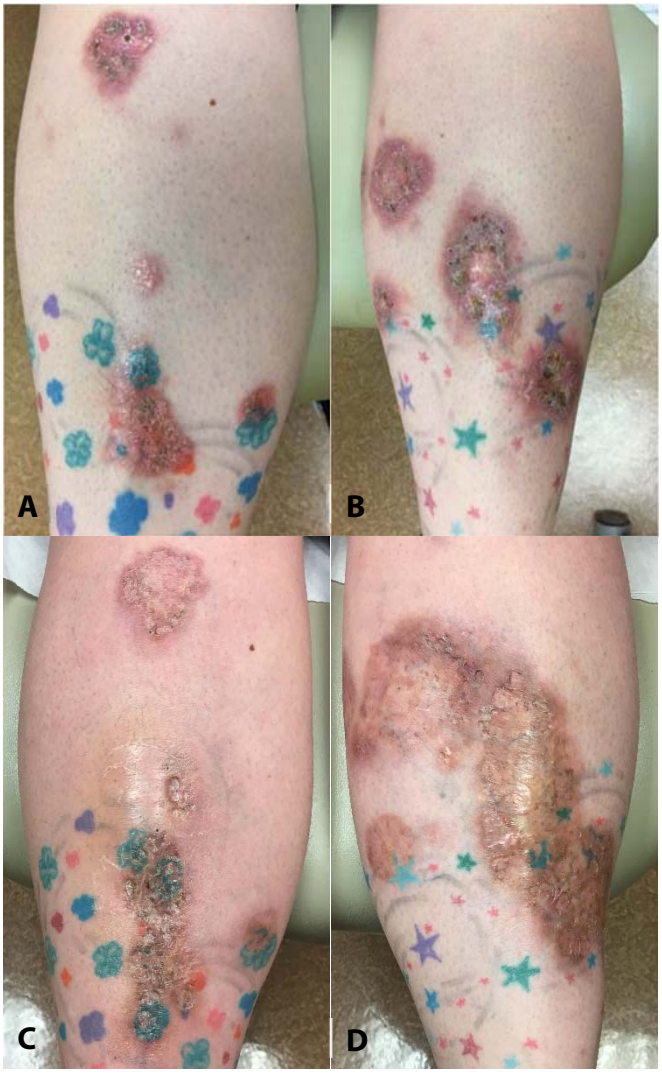

Figure 1. *Lesions of the right lower leg **A)** and left lower leg **B)** on the patient's initial visit to our office. Post inflammatory changes and improvement of the erythema and ulcerations of the right lower leg **C)** and left lower leg **D)** after 6 weeks of treatment with ustekinumab (7 months after the initial visit to our office).*

Case Discussion

Many of the challenges in treating necrobiosis lipoidica are likely related to the unclear pathophysiology of the disease. The broad spectrum of histological findings between individuals suggests a multifactorial etiology and may be the reason for diverse treatment responses [17]. Histopathological findings can also differ at different times of the course of the disease, as it did in our patient, with an earlier biopsy showing more of a non-specific reactive process. Diagnosis and effective treatment were delayed as a result. Our patient's risk factors of smoking, hypertension, uncontrolled diabetes, and history of repeated wound infections also likely played a role in poor treatment response.

The scientific literature for the treatment of necrobiosis lipoidica mostly consists of case reports and small clinical trials [19]. Topical, systemic, and intralesional steroids are often used as a first line treatment with varying responses. [20-22]. Topical tacrolimus, PUVA, photodynamic therapy,

antimalarials, immunomodulators, biologic agents, IVIG, topical tretinoin, hyperbaric oxygen therapy, and cutaneous blood flow modulators are just some of the treatments that have all been reported [23-34]. Whether diabetic glycemic control improves necrobiosis lipoidica has not yet been supported by studies, but could theoretically help wound healing, improve vascular function, and prevent superinfection [35]. Emphasizing smoking cessation and avoidance of trauma can also help reduce complications [35, 36].

Anti-TNF agents, in particular, are effective in treating granulomatous disease and have been successfully used as monotherapy in treating ulcerating necrobiosis lipoidica [13, 29, 37]. Given our patient's adverse reaction to adalimumab and treatment failure for most therapies, we elected to utilize ustekinumab, an IL12 and IL23 inhibitor typically used to treat psoriasis [38]. Ustekinumab was successfully used for one case of necrobiosis lipoidica in our practice in an individual without diabetes in the past [18]. The intention behind using ustekinumab was to target the Th1 pathway to limit granuloma formation. A proposed mechanism by which ustekinumab treats necrobiosis lipoidica may be related to its ability to target the Th1 pathway through IL12 inhibition. Th1 cells, which require IL12, interact with macrophages in a CD40-CD40L-dependent manner, leading to IFNγ secretion. Interferon γ binds to the macrophage receptors, activating them and promoting TNF formation, leading to granuloma formation. Interleukin 23 inhibition of Th17 cells by ustekinumab may also account for its effectiveness in necrobiosis lipoidica, as these cells have been found in skin lesions of necrobiosis lipoidica [39-41].

Conclusion

Necrobiosis lipoidica is a complex disease of multifactorial etiology. A tailored treatment approach for the individual is necessary. Ustekinumab may be an effective treatment for treatment-resistant necrobiosis lipoidica. Given challenges in treating necrobiosis lipoidica and limited data on effective therapies, further clinical studies for the use of ustekinumab in the treatment of necrobiosis lipoidica are required.

Potential conflicts of interest

RKS serves a medical editor for LearnHealth and as a consultant for Burts' Bees, Dermala, and Tomorrow's Leaf. The remaining author declares no conflicts of interests.

References

1. Muller SA, Winkelmann RK. Necrobiosis lipoidica diabeticorum. A clinical and pathological investigation of 171 cases. *Arch Dermatol*. 1966;93:272-81. [PMID: 5910868].
2. Erfurt-Berge C, Seitz AT, Rehse C, et al. Update on clinical and laboratory features in necrobiosis lipoidica: a retrospective multicentre study of 52 patients. *Eur J Dermatol*. 2012;22:770-5. [PMID: 23114030].
3. O'Toole EA, Kennedy U, Nolan JJ, et al. Necrobiosis lipoidica: only a minority of patients have diabetes mellitus. *Br J Dermatol*. 1999;140:283-6. [PMID: 10233223].
4. Peyri J, Moreno A, Marcoval J. Necrobiosis lipoidica. *Semin Cutan Med Surg*. 2007;26:87-9. [PMID: 17544959].
5. Magro CM, Crowson AN, Regauer S. Granuloma annulare and necrobiosis lipoidica tissue reactions as a manifestation of systemic disease. *Hum Pathol*. 1996;27:50-6. [PMID: 8543311].
6. Jockenhofer F, Kroger K, Klode J, et al. Cofactors and comorbidities of necrobiosis lipoidica: analysis of the German DRG data from 2012. *J Dtsch Dermatol Ges*. 2016;14:277-84. [PMID: 26972191].
7. Imtiaz KE, Khaleeli AA. Squamous cell carcinoma developing in necrobiosis lipoidica. *Diabet Med*. 2001;18:325-8. [PMID: 11437865].
8. Kota SK, Jammula S, Kota SK, et al. Necrobiosis lipoidica diabeticorum: A case-based review of literature. *Indian J Endocrinol Metab*. 2012;16:614-20. [PMID: 22837927].
9. Oikarinen A, Mortenhumer M, Kallioinen M, Savolainen ER. Necrobiosis lipoidica: ultrastructural and biochemical demonstration of a collagen defect. *J Invest Dermatol*. 1987;88:227-32. [PMID: 3805759].
10. Ullman S, Dahl MV. Necrobiosis lipoidica. An immunofluorescence study. *Arch Dermatol*. 1977;113(12):1671-3. [PMID: 596895].
11. Holland C, Givens V, Smoller BR. Expression of the human erythrocyte glucose transporter Glut-1 in areas of sclerotic collagen in necrobiosis lipoidica. *J Cutan Pathol*. 2001;28:287-90. [PMID: 11401674].
12. Ngo B, Wigington G, Hayes K, et al. Skin blood flow in necrobiosis lipoidica diabeticorum. *Int J Dermatol*. 2008;47:354-8. [PMID: 18377597].
13. Sibbald C, Reid S, Alavi A. Necrobiosis Lipoidica. *Dermatol Clin*. 2015;33:343-60. [PMID: 26143418].

14. Llajam MA. Koebner's phenomenon and necrobiosis lipoidica diabeticorum. *Br J Clin Pract*. 1990;44:765. [PMID: 2102235].
15. Gebauer K, Armstrong M. Koebner phenomenon with necrobiosis lipoidica diabeticorum. *Int J Dermatol*. 1993;32:895-6. [PMID: 8125696].
16. Patel GK, Harding KG, Mills CM. Severe disabling Koebnerizing ulcerated necrobiosis lipoidica successfully managed with topical PUVA. *Br J Dermatol*. 2000;143:668-9. [PMID: 10971363].
17. Yen P-Sea. The many faces of necrobiosis lipoidica: a report of three cases with histologic variations. *Dermatologica Sinica*.29:67-71. [DOI:10.1016/j.dsi.2011.05.006].
18. Hassoun LA, Sivamani RK, Sharon VR, et al. Ustekinumab to target granulomatous dermatitis in recalcitrant ulcerative necrobiosis lipoidica: case report and proposed mechanism. *Dermatol Online J*. 2017;23(7). [PMID: 29469709].
19. Feily A, Mehraban S. Treatment Modalities of Necrobiosis Lipoidica: A Concise Systematic Review. *Dermatol Reports*. 2015;7:5749. [PMID: 26236446].
20. Goette DK. Resolution of necrobiosis lipoidica with exclusive clobetasol propionate treatment. *J Am Acad Dermatol*. 1990;22(5 Pt 1):855-6. [PMID: 2347975].
21. Taniguchi Y, Sakamoto T, Shimizu M. A case of necrobiosis lipoidica treated with systemic corticosteroid. *J Dermatol*. 1993;20:304-7. [PMID: 8340536].
22. Sparrow G, Abell E. Granuloma annulare and necrobiosis lipoidica treated by jet injector. *Br J Dermatol*. 1975;93:85-9. [PMID: 1191532].
23. Harth W, Linse R. Topical tacrolimus in granuloma annulare and necrobiosis lipoidica. *Br J Dermatol*. 2004;150:792-4. [PMID: 15099394].
24. De Rie MA, Sommer A, Hoekzema R, Neumann HA. Treatment of necrobiosis lipoidica with topical psoralen plus ultraviolet A. *Br J Dermatol*. 2002;147:743-7. [PMID: 12366422].
25. Kavala M, Sudogan S, Zindanci I, et al. Significant improvement in ulcerative necrobiosis lipoidica with hydroxychloroquine. *Int J Dermatol*. 2010;49:467-9. [PMID: 20465710].
26. West EA, Warren RB, King CM. A case of recalcitrant necrobiosis lipoidica responding to combined immunosuppression therapy. *J Eur Acad Dermatol Venereol*. 2007;21:830-1. [PMID: 17567321].
27. Reinhard G, Lohmann F, Uerlich M, et al. Successful treatment of ulcerated necrobiosis lipoidica with mycophenolate mofetil. *Acta Derm Venereol*. 2000;80:312-3. [PMID: 11028876].
28. Barde C, Laffitte E, Campanelli A, et al. Intralesional infliximab in noninfectious cutaneous granulomas: three cases of necrobiosis lipoidica. *Dermatology*. 2011;222:212-6. [PMID: 21625077].
29. 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;221:117-21. [PMID: 20805688].
30. Batchelor JM, Todd PM. Treatment of ulcerated necrobiosis lipoidica with intravenous immunoglobulin and methylprednisolone. *J Drugs Dermatol*. 2012;11:256-9. [PMID: 22270213].
31. Heymann WR. Necrobiosis lipoidica treated with topical tretinoin. *Cutis*. 1996;58:53-4. [PMID: 8823549].
32. Bouhanick B, Verret JL, Gouello JP, et al. Necrobiosis lipoidica: treatment by hyperbaric oxygen and local corticosteroids. *Diabetes Metab*. 1998;24:156-9. [PMID: 9592641].
33. Karkavitsas K, Miller JA, Dowd PM, Kirby JD. Aspirin iin the management of necrobiosis lipoidica. *Acta Derm Venereol*. 1982;62:183. [PMID: 6179354].
34. De Giorgi V, Buggiani G, Rossi R, et al. Successful topical photodynamic treatment of refractory necrobiosis lipoidica. *Photodermatol Photoimmunol Photomed*. 2008;24:332-3. [PMID: 19000193].
35. Reid SD, Ladizinski B, Lee K, et al. Update on necrobiosis lipoidica: a review of etiology, diagnosis, and treatment options. *J Am Acad Dermatol*. 2013;69:783-91. [PMID: 23969033].
36. Kelly WF, Nicholas J, Adams J, Mahmood R. Necrobiosis lipoidica diabeticorum: association with background retinopathy, smoking, and proteinuria. A case controlled study. *Diabet Med*. 1993;10:725-8. [PMID: 8261754].
37. Hu SW, Bevona C, Winterfield L, et al. Treatment of refractory ulcerative necrobiosis lipoidica diabeticorum with infliximab: report of a case. *Arch Dermatol*. 2009;145:437-9. [PMID: 19380665].
38. Krulig E, Gordon KB. Ustekinumab: an evidence-based review of its effectiveness in the treatment of psoriasis. *Core Evid*. 2010;5:11-22. [PMID: 20694136].
39. Alunno A, Carubbi F, Cafaro G, et al. Targeting the IL-23/IL-17 axis for the treatment of psoriasis and psoriatic arthritis. *Expert Opin Biol Ther*. 2015;15:1727-37. [PMID: 26653110].
40. Kato M, Oiso N, Itoh T, et al. Necrobiosis lipoidica with infiltration of Th17 cells into vascular lesions. *J Dermatol*. 2014;41:459-61. [PMID: 24801926].
41. Nakamura-Wakatsuki T, Yamamoto T. Palmoplantar pustulosis associated with necrobiosis lipoidica: a possible role of tumor necrosis factor-alpha and interleukin-17. *J Dermatol*. 2014;41:461-2. [PMID: 24628381].