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Case Report

Dupilumab as a Novel and Effective Treatment for Refractory Necrobiosis Lipoidica

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Introduction

Necrobiosis lipoidica (NL) is a chronic granulomatous skin disorder that affects the lower extremities, predominantly the shins. It presents most commonly as defined and persistent round or irregular telangiectatic plaques. Although NL is considered idiopathic, it has been reported to be associated with diabetes mellitus [1]. Among those diagnosed with diabetes mellitus, only 0.3% also suffer from necrobiosis lipoidica [2]. While no single treatment has been proven superior, systemic, intralesional, and topical steroids have been utilized with variable efficacy [3]. Here, we report the first case of NL in the setting of type 1 diabetes refractory to numerous first-line therapies demonstrating rapid and complete response to treatment with subcutaneous dupilumab injections.

Case report

A 42-year-old woman presented with a ten-year history of annular papules and plaques on her bilateral shins (Figure 1A). She had been diagnosed with type 1 diabetes twenty years ago, which has been well-controlled with insulin injections. The patient denied any pain, pruritus, tenderness, or ulceration of the affected areas. However, she reported adverse psychosocial effects, decreased self-confidence, and not wanting to expose her lower legs in public. Multiple skin biopsies over ten years had demonstrated palisading granuloma correlating with the clinical presentation of NL. Numerous therapies tried and failed over the ten years included monotherapy and multitherapy combinations with oral methotrexate, oral pentoxifylline, oral hydroxychloroquine, oral doxycycline, oral dapsone, oral tofacitinib, various low and high potency topical corticosteroids, topical crisaborole, intralesional triamcinolone injections, intense pulsed light therapy, and nbUVB light therapy. The patient had the most significant but temporary improvement with recurrent intralesional triamcinolone injections. However, she developed one episode of diabetic ketoacidosis six years into her NL disease in addition to recurrent steroid-induced hypopigmentation and atrophy from intralesional steroid injections over time. Therefore, intralesional triamcinolone injections were not used from 2016 to 2020. While maintained on oral hydroxychloroquine and topical betamethasone dipropionate ointment for several years, NL plaques persisted without remission (Figure 1B).

Given her refractory and persistent disease, treatment with dupilumab injections as a new alternative to target inflammation was recommended. She was started on subcutaneous dupilumab injections, a biologic agent that blocks the signaling of IL-4 and IL-13, limiting the inflammatory response of T helper cells [4]. Based on past temporary improvement from intralesional triamcinolone, 3 ml of intralesional triamcinolone 10 mg/ml were injected into the NL plaques once at the start of dupilumab therapy in an effort to augment the anti-inflammatory response of the treatment. Remarkably, within one month of this one-time treatment combination, the lesions significantly improved (Figure 1C). After the dupilumab starting dose of 600 mg, the patient administered dupilumab 300 mg injection subcutaneously every 2 weeks with no adverse side effects from the therapy. Hydroxychloroquine and topical betamethasone application were stopped at three months of dupilumab treatment due to complete and sustained remission of disease. She has no recurrent NL plaques after five months of monotherapy with dupilumab. Clinical presentation at the time of publication reflects residual scarring and discoloration on the patient's shins from past skin lesions and a complete response to treatment (Figure 1D).

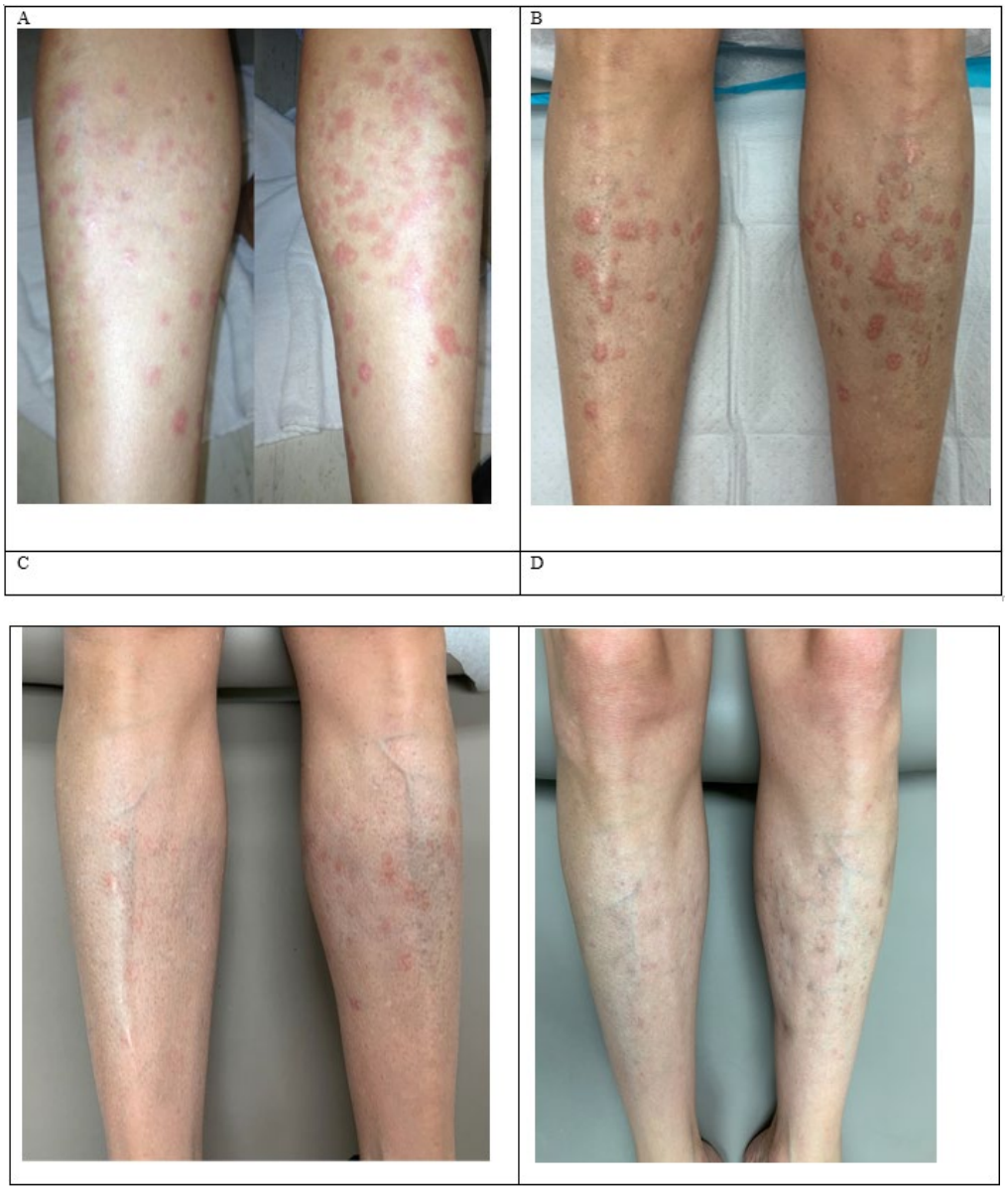

Figure 1: A: Necrobiosis lipoidica in 2010 at onset of disease with well-defined inflammatory plaques affecting both shins. **B:** Persistent skin lesions in 2020 prior to dupilumab injection. **C:** Significant improvement one month after dupilumab treatment. **D:** Residual scarring and atrophy of shins with no active NL lesions after eight months of treatment with dupilumab.

Discussion

Necrobiosis lipoidica (NL) is a rare skin condition defined by plaques predominantly on the lower extremities of unknown etiology [5]. Originally referred to as necrobiosis lipoidica diabeticorum, NL is associated with diabetes mellitus but this endocrine disorder is not necessary for the development of NL [6]. In our case, the patient is a twenty-year insulin-dependent type 1 diabetic female. Even though reported treatment options for NL range in efficacy, systemic and topical steroids provide the most immediate improvement [3]. There is concern about continued oral and intralesional steroid use in diabetic patients due to insulin resistance and potential complications from elevated blood sugar levels. Thus, effective non-steroid treatments may be most beneficial to diabetic patients with NL and could eliminate complications, such as diabetic ketoacidosis, experienced by our patient from the use of intralesional steroids.

Dupilumab is a FDA-approved injectable therapy to treat inflammatory conditions such as atopic dermatitis, asthma, and chronic rhinosinusitis by blocking the signaling of IL-4 and IL-13, thus blocking cytokines from inducing an immune response [7]. Similarly to atopic dermatitis, NL is classified as an inflammatory condition with abnormal immune activation of T helper cells [8,9]. Therefore, dupilumab's mechanism of action may support effective clinical treatment of NL and be beneficial as a non-steroid treatment for NL with or without diabetes. Similar to atopic dermatitis treatment with dupilumab, rapid cutaneous lesion clearance and reduction in visible inflammation was demonstrated after an initial subcutaneous injection of 600 mg and subsequent maintenance injection of 300 mg every two weeks with no recurrence of disease.

Conclusion

Necrobiosis lipoidica is a rare inflammatory disorder associated with diabetes mellitus. In this case report, a patient with a ten-year history of refractory NL was successfully treated with dupilumab, a biologic agent that blocks the signaling of IL-4 and IL-13. Her disease remains in full remission after eight months of treatment and may be a result of dupilumab limiting the inflammatory response of T helper cells. Further investigation is needed to study dupilumab as a safe and effective first-line therapy for NL and as a potential treatment for other related granulomatous disorders, such as granuloma annulare, necrobiotic xanthogranuloma, sarcoidosis, and erythema nodosum.

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