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Case Report

Atypical Ulcerative Necrobiosis Lipoidica Diabeticorum: A Case Study

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Abstract

Necrobiosis lipoidica is a granulomatous skin condition commonly associated with diabetes. When associated with diabetes mellitus, the name expands to necrobiosis lipoidica diabeticorum (NLD). In these patients, this rare condition has an incidence rate of 0.3% to 1.6%. The cause of NLD remains unknown even though many speculations exist in the medical literature. The treatment of this condition has most researchers agreeing on the use of topical steroids for the anti-inflammatory effect on NLD; however, the role of glucose control in the treatment of this disorder has been debatable. The following case presents a patient who, despite better glucose control, did not improve until the introduction of doxycycline.

Keywords

necrobiosis lipoidica, diabetes mellitus, glucose control, doxycycline

Introduction

Necrobiosis lipoidica (NL) is a rare inflammatory granulomatous skin condition commonly associated with diabetes but can be present in nondiabetic patients. When it occurs in diabetic patients, the name changes to necrobiosis lipoidica diabeticorum (NLD). The incidence rate in these patients, typically quoted, ranges from 0.3% to 1.6%.[1,2] It presents more commonly in women than in men.[3] The skin disorder has reddish-brown plaques with the center turning yellow and developing atrophy. Ulceration can happen within these plaques, and when it does, pain results. It occurs more commonly on the anterior surface of legs but can occur on other areas of the body including the arms, the head, and the trunk.

There continues to be speculation on the cause and treatment of NLD. Most authors agree microangiopathy plays some role in this condition.[4,5] However, without a full understanding of the disorder, treatment can be difficult to establish. Not surprisingly, the treatment for it remains controversial.[4,6] Although most researchers agree on topical steroids,[4] past literature questioned the improvement of this skin condition with tighter glucose control. More recent case studies suggest it may help resolve NLD.[7]

The following case report is of an atypical NLD patient whose improvement did not correlate with better glucose control but only with treatment of doxycycline. The patient gave permission by written informed consent to publish the case details and associated images.

Case

A 57-year-old Hispanic diabetic woman with renal insufficiency, hypertension, and hypothyroidism presented to the office with small bilateral eschars. The patient stated these eschars initially started as small erythematous bumps, the size of mosquito bites, without pain, and very pruritic. The bumps grew, ulcerated, and she developed eschars. It became too painful to walk and she needed a wheelchair to get around. The patient mentioned she had a similar episode 7 years ago. According to her, she had debridement performed at that time and the lesions healed. Her physician in Puerto Rico placed her on pentoxifylline, which she has continued to use and has had no lesions until now.

Initially, on physical examination, the patient had small areas of fixed eschars on her bilateral legs. Her hemoglobin A1c (HgbA1c) at this visit was 9.5% (normal range = 4.5% to 5.6%). Her treatment for her diabetes consisted of the following medications: glipizide, insulin aspart (Novolog-Novo Nordisk), insulin glargine (Toujeo-Sanofi), and linagliptin (Trajente-Boehringer Ingelheim). In spite of these medications, the patient's control of her blood sugar remained poor. The patient admitted to the need to be better

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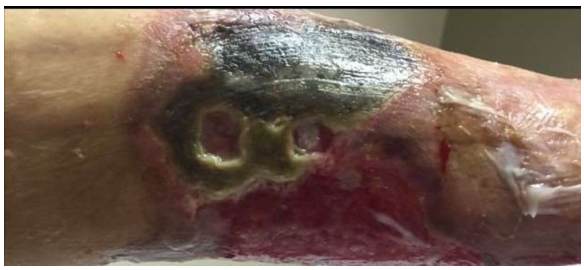

Figure 1. Necrobiosis lipoidica of the left medial lower leg with dry black eschars and ulceration.

with her diabetic control through her diet. Her ankle-brachial index of the right leg measured at 1.0, and the left leg measured at 1.1. The eschars were removed by sharp debridement and covered with foam dressings. Four months later, in spite of her improving HgbA1c of 8.4%, her wounds worsened with ulcerations (Figures 1 and 2). The bilateral arterial ultrasound of her legs showed triphasic waveforms throughout her lower extremities. Her bilateral venous ultrasound of her legs revealed minimal reflux of both legs only at the saphenofemoral junction. The patient continued to receive weekly wound care with debridement, foam dressings, and 2-layer compression wraps.

One month later, the wounds on the left leg developed wet necrotic eschars with ulcerations (Figure 3). Her tibia/fibula X-ray showed vascular calcifications only. A punch biopsy of 0.5 cm in depth, performed on the ulcer edge of the left lower posterior leg, showed extensive gangrenous necrosis, neutrophilic infiltration, and dermolysis. The tissue blood vessels had chronic diabetic microangiopathic changes. The left lower medial leg punch biopsy with the same depth as the posterior aspect of the same leg showed a denuded epidermis with edema below it containing hyalinizing laminated pattern of fibrosis. Lymphocytes, multinucleated histiocytes, plasma cells, and neutrophils were present with neovascularization. Other findings included nodular aggregates of lymphocytes and chronic microangiopathic changes. The tissue sample also had calcification noted within the nerve.

A culture of the left leg after debridement resulted in moderate *Pseudomonas aeruginosa* and moderate *Staphylococcus aureus* growth. Since the patient's white blood cell count was only 10 400/mL (normal range = 4000/mL to 10 000/mL), with the differential only showing a slight elevation of monocytes, a normal procalcitonin level, and no symptoms of fever or abnormal erythema indicative of infection, a diagnosis of critical colonization resulted. In accordance with this diagnosis, topical treatment of antimicrobial collagen (Endoform AM of Aroa BioSurgery Ltd) began with a super absorbent dressing (Xtrasorb of DermaSciences) for drainage.

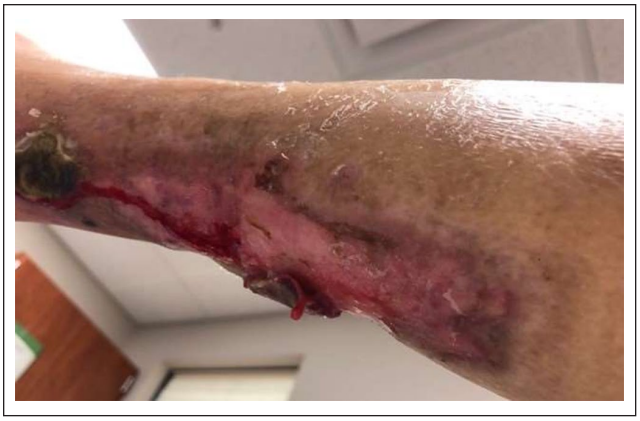

Figure 2. Necrobiosis lipoidica of the left posterior lower leg with dry black eschars.

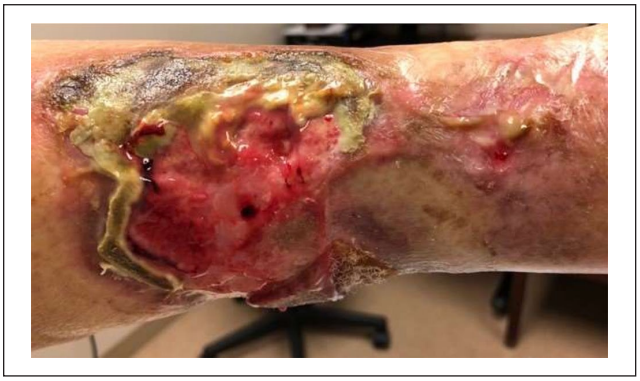

Figure 3. The left medial lower leg with wet necrotic eschars, ulcerations, and signs of *Pseudomonas* overgrowth.

Dermatology and Rheumatology consults were ordered. The rheumatologist ordered an extensive vasculitis workup, which had negative results. The dermatologist believed the ulcers were caused by an inflammatory state. He started her on doxycycline 100 mg by mouth twice a day to decrease inflammation not for its antimicrobial properties. The topical steroid clobetasol had been prescribed; however, the patient never filled it due to cost. He consulted infectious disease, who agreed with treating the legs with topical gentamicin antibiotics as a result of the culture. This application occurred 1 to 2 times a week with dressing changes of the left leg.

A discussion of the possible diagnosis of NLD resulted since the biopsy revealed microangiopathy, multinucleated histiocytes, plasma cells, neutrophils, and nodular aggregates of lymphocytes. It was hypothesized that the biopsy did not have the classic feature of this skin condition, palisading granulomas, since the tissue had progressed to extensive necrosis, which made this case an atypical presentation of NLD. The pathologist later confirmed this hypothesis. The patient started to improve less than 1

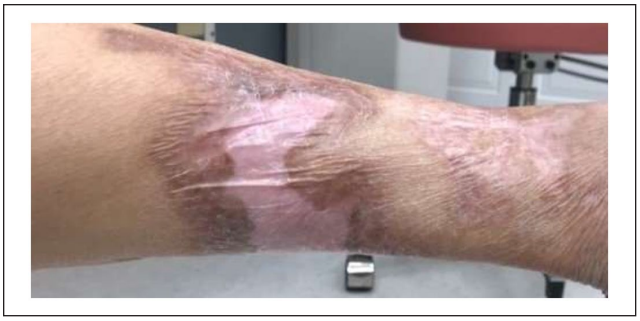

Figure 4. Left medial lower leg—closed wounds.

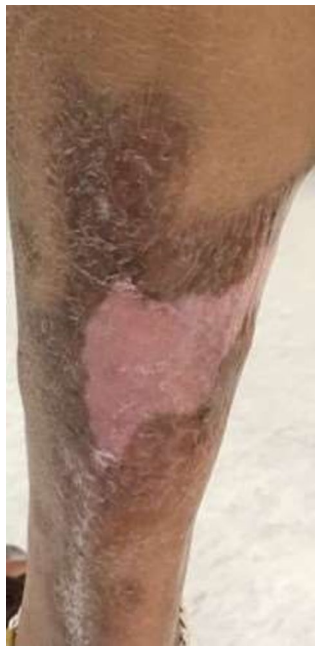

Figure 5. Left posterior lower leg—closed wounds.

month after doxycycline use, with the right lower leg wounds closing, improvement of the left lower leg wounds, and complete resolution of the left lower leg wounds after 4 months (Figures 4 and 5). The patient remains symptom-free, follows up with dermatology for skin checks and takes doxycycline in a tapering dose, which originally started at 100 mg by mouth twice a day for 6 months, then decreased to 100 mg 3 times a week for 6 months, then 100 mg twice a week for 6 months, and finally, 100 mg once a week for 6 months. Triamcinolone acetonide 0.1% had been added after resolution of the lesions for the occasional leg itching.

Discussion

This rare condition called necrobiosis lipoidica was first described by Maurice Oppenheim in 1929 to the Dermatology Society of Vienna. He presented the clinical course and histological findings of the new disorder. He described the condition in German as a "peculiar disseminated degeneration of connective tissue of the skin of a diabetic,"[8] and later shortened the description to an "actual connective tissue degeneration."[8] However, his histological findings did not include lipoid inhibition of the tissue. In 1932, Erich Urbach presented the case of a patient with NL to the same society making note of the lipoid changes in the tissue. Due to these findings, he used the name necrobiosis lipoidica diabeticorum in his publication on the condition.[8] Since then, the name has changed by the removal of diabeticorum for those patients without diabetes and at times, for those with diabetes, likely for consistency's sake.

There have been multiple suggestions for the cause of NL, but it remains unknown. When associated with diabetes mellitus, some argue[6] the pathogenesis in this disorder involves diabetic microangiopathy. However, this theory does not explain NL in patients without diabetes. Another theory mentioned involves abnormal collagen production,[9] since this condition affects the dermis resulting in a breakdown of collagen and elastin along with a decrease in the production of collagen.[3] In spite of all the theories, in the end, there are likely multiple factors involved in the cause of NL in patients with and without diabetes.

The histological findings present in NLD include palisading granulomas, a classic sign, which contain histiocytes, multinucleated lymphocytes, plasma cells, and eosinophils.[9] Lymphocytes are also noted in aggregates in the dermis.[10] When ulceration occurs, neutrophils are usually seen.[11] The epidermis can be unaffected or atrophic.[12] Blood vessels tend to have similar findings, seen with diabetic microangiopathy, such as blood vessel wall thickening.[9]

The histologic findings in this patient had the common features seen in NLD. These features included aggregates of lymphocytes, plasma cells, microangiopathy,[6] and multinucleated histiocytes. Since this patient had ulceration of her wounds, neutrophils were also noted. Due to the fact the tissue had gangrenous necrosis, the classic sign of palisading granulomas could not be visualized; although, the cell types normally contained within them were present, making this an atypical presentation of NLD.

Several diagnoses had been considered in the differential. Some of these possibilities included venous ulcers, arterial ulcers, ulcers caused by calciphylaxis, and skin changes due to diabetic dermopathy. The patient did not have a clinical picture of venous or arterial ulcers, which was reinforced by minimal reflux only at the saphenofemoral junction in her bilateral legs on venous ultrasound and a normal arterial ultrasound with triphasic waveforms throughout her lower extremities. These findings resulted in dismissal of these diagnoses. Diabetic dermopathy, a skin disorder that occurs mainly on the shins, was also considered. The vascular complications associated with it include

diabetic microangiopathy as seen in this patient. However, the lesions in diabetic dermopathy do not result in ulceration and do not usually require treatment except to manage tighter glucose control. Since the patient had ulcerations of her lesions and these lesions worsened with tighter glucose control, this diagnosis could not be attributed to the patient's lesions.

Calciphylaxis, a condition causing vascular calcification leading to ischemic necrosis of tissue, had been considered in the differential diagnosis of this patient for 2 reasons. The patient had pain out of proportion for her wounds and the pathology report noted the finding of calcification within a nerve. However, the patient had multiple findings inconsistent with this diagnosis. She only had mild renal dysfunction; although this can be seen in calciphylaxis, it is rare. She had a normal calcium level, no obesity, and no hypercoagulability states. Her laboratory test results and her clinical picture, which included a lack of subcutaneous calcification on X-ray and the lack of other histological findings, such as microthrombi, prompted the dismissal of the diagnosis.

The dermatologist, in agreement with the infectious disease specialist, placed the patient on topical gentamycin due to *Pseudomonas aeruginosa* and *Staphylococcus aureus* growth on her lesions. Since the patient only used this topical antibiotic with dressing changes that occurred twice a week, the antibiotic would have had no effect in treating the bacteria. The frequency would need to be at a minimum of 3 times a day due to its half-life of 2 to 4 hours. Critical colonization resulted in bacteria overgrowth in the wound, which required local treatment with antimicrobial dressings and sharp debridement. Infection had been ruled out due to a normal procalcitonin level, a white blood cell count of 10 400/mL with a differential only showing elevated monocytes, and no fever or abnormal erythema indicative of infection. The elevation in monocytes supported the wound being caused by an inflammatory state.

There have been multiple treatments suggested for NLD including topical and intralesional steroids. Steroid use is common with nonulcerated lesions because they decrease the inflammation seen in NLD and can be combined with other treatments to promote healing of the lesions.[13] Steroids need to be used with caution near atrophic skin, since they can cause ulceration. Care also needs to be used when placing topical steroids under an occlusion dressing because this has also been shown to lead to ulceration.[14] Pentoxifylline, antitumor necrosis factor-α therapy, ultraviolet A1 phototherapy, aspirin, dipyridamole (antiplatelet therapy), topical tacrolimus, and fumaric acid esters are additional treatments that have been suggested.[6,13] Since steroid use can make ulcerated lesions worse, other treatments need to be considered when dealing with these types of lesions. These treatments can include several mentioned above and others like doxycycline, hydroxychloroquine, and colchicine.[13]

In this case, the patient had already been using a suggested treatment for NLD. The patient was taking pentoxifylline when the lesions developed and the wounds worsened while she was taking the medication, leading to the conclusion, that for this patient, the medication did not have a benefit. She also had been on aspirin in the past. When questioned directly on her use of the topical steroids, the patient admitted she never used them due to the cost. Due to her worsening ulcerations, the lack of topical steroid use likely prevented further deterioration of these wounds.

Tighter glucose control in patients with NLD has been debated as a treatment focus. There have been a few case reports that show NLD improving with better glucose control.[7] However, in this case, 5 months after the time of presentation to the office, the patient's HgbA1c went from 9.5% to 8.4% and the wounds significantly worsened, showing tighter glucose control did not have an impact on the improvement of the lesions in this patient. There are no large studies that confirm the finding of glucose control improving NLD.[7] It may be difficult to conduct a large study with a rare condition such as this. It has also been previously shown that many NLD patients have elevated HgbA1c at time of presentation,[13] as in this patient, which seems to suggest glucose control playing a role in NLD, but this finding may simply be a reactionary stress response over time to this skin condition. At this point, the relationship between the elevated HgbA1c at time of presentation and NLD remains elusive.

The treatment with doxycycline caused a dramatic improvement in the patient's condition. This effect could not be attributed to treatment of infection, since the patient did not have symptoms or signs of infection, as previously stated. It should also be noted that doxycycline did not show sensitivity to *Pseudomonas* on culture, so improvement of the wound would not be expected from this antibiotic. The patient was in a significant amount of pain at the beginning of treatment, to the point she used a wheelchair because the pain prohibited her ability to walk. However, after starting on doxycycline, her left lower leg wounds improved in less than 1 month of treatment and her right lower leg wounds closed. Her pain improved after 2 months of doxycycline treatment and she was soon able to walk without a wheelchair. After 4 months of treatment with doxycycline, the left lower leg wounds closed, and the patient did not have a recurrence after 32 months of follow-up.

Her HgbA1c at the time of closure decreased to 7.3%. However, the patient's steady improvement of her HgbA1c (9.5% to 7.3%) did not correlate with wound improvement until after doxycycline had been started. These results are similar to a recent pediatric case report showing resolution of NLD with doxycycline treatment.[15] The major difference between these patients dealt with the glucose control

with the pediatric patient having poor glucose control throughout the course of treatment and this patient having improved glucose control. This finding further emphasizes the significant effect doxycycline can have on these lesions.

Although doxycycline typically is used for its antimicrobial properties, it has multiple other functions that help decrease inflammation and promote wound healing. Doxycycline has been shown to inhibit bacterial factors causing inflammation, to suppress migration of neutrophils and chemotaxis, to decrease matrix metalloproteinases, to suppress proinflammatory cytokines, to inhibit the formation of granulomas, and to inhibit nitric oxide synthetase.[16,17] In this patient, if doxycycline had been treating infection, resolution of all the lesions would be expected in less than 4 months. In this case, doxycycline's anti-inflammatory properties worked effectively in resolving her lesions.

Conclusion

In this atypical case of NLD, glucose control, although known to improve wound healing, did not play a significant role in improving the wounds in this patient. In fact, the lesions worsened in spite of better glucose control, but resolution of the lesions occurred with the use of doxycycline. Therefore, it does not add to other case reports showing resolution of NLD with tighter glucose control. It does add to the recent pediatric case report showing dramatic resolution of these lesions with doxycycline.

Declaration of Conflicting Interests

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