

REVIEW PAPER

ARTYKUŁ PRZEGLADOWY

**NECROBIOSIS LIPOIDICA – A RARE DISEASE CAUSING THERAPEUTIC
DIFFICULTIES: A REVIEW OF AVAILABLE AND POTENTIAL TREATMENTS**

**OBUMIERANIE TŁUSZCZOWATE – RZADKA JEDNOSTKA CHOROBY
POWODUJĄCA TRUDNOŚCI TERAPEUTYCZNE: PRZEGLĄD DOSTĘPNYCH
I POTENCJALNYCH METOD LECZENIA**

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Summary

Necrobiosis lipoidica (NL) is a rare, chronic granulomatous condition occurring mostly on the skin of the pretibial area in middle-aged woman. Only 0.3% of diabetic patients will develop NL, but about 60% of patients with NL are diabetic. NL can coexist with other diseases such as: thyroiditis, inflammatory bowel disease, sarcoidosis, obesity, dyslipidemia, hypertension, coronary heart disease, stroke, and reduced renal function. There are multiple theories regarding the etiopathogenesis of NL, but it still remains unknown. Scientific data regarding treatment for NL consists mostly of case reports and rather small clinical trials. To this day, no uniform therapeutic recommendations have been created. Topical and intralesional corticosteroids have been the first-line treatment for active, enlarging NL lesions for years. Therapies such as calcineurin inhibitors, retinoids, systemic corticosteroids, and many more have been used with various results. Currently, no single therapy method is superior to another, though some of them seem to stand out. JAK inhibitors, TNF- α inhibitors and light therapies, among others, have been showing the most promising results in NL treatment. Despite good treatment results, further studies are required to establish real efficacy and the safety of each method and create uniform therapeutic guidelines for NL treatment.

Keywords: necrobiosis lipoidica, JAK inhibitors, phototherapy, ulceration, treatment

Streszczenie

Obumieranie tłuszczowate (OT) to rzadka, przewlekła choroba ziarniniakowa, powstająca głównie na skórze łydki u kobiet w średnim wieku. Jedynie 0,3% pacjentów z cukrzycą rozwinię OT, ale aż 60% pacjentów z OT choruje na cukrzycę. OT może współistnieć także z innymi chorobami, takimi jak: zapalenie tarczycy, choroby zapalne jelit, sarkoidoza, otyłość, dyslipidemia, nadciśnienie, choroba wieńcowa, udar, niewydolność nerek. Istnieje wiele teorii dotyczących patogenezy tej choroby, ale ostatecznie pozostaje ona niewyjaśniona. Dane naukowe dotyczące leczenia OT pochodzą głównie z opisów przypadków klinicznych i badań na małych grupach pacjentów. Do dnia dzisiejszego nie powstały jednorodne rekomendacje dotyczące leczenia OT. Steroidy stosowane miejscowo oraz w formie iniekcji od dawna stanowią leczenie pierwszego wyboru dla aktywnych, powiększających się zmian spowodowanych OT. Metody leczenia takie jak: inhibitory kalcyneuryny, retinoidy, sterydy podawane systemowo i wiele innych były stosowane z różnymi rezultatami. Obecnie żadna terapia nie wydaje się być znacząco lepsza od innych, ale część opisywanych terapii zdaje się wyróżniać. Inhibitory kinaz janusowych, inhibitory TNF- α , czy terapie wykorzystujące światło wykazują najbardziej obiecujące wyniki w leczeniu OT. Mimo dobrych efektów terapeutycznych, istnieje konieczność przeprowadzenia dalszych badań, w celu określenia skuteczności i bezpieczeństwa każdej z metod oraz stworzenia wytycznych dotyczących leczenia OT.

Słowa kluczowe: obumieranie tłuszczowate, inhibitory JAK, fototerapia, owrzodzenie, leczenie

Introduction

Necrobiosis lipoidica (NL) is a rare, chronic granulomatous condition occurring mostly on the skin of the pretibial area in middle-aged woman. Traditionally, NL has been considered as a specific manifestation of diabetes, thus, in literature, it used to be called necrobiosis lipoidica diabetorum (NLD) [1]. It is worth paying attention to the fact that only 0.3% of diabetic patients will develop NL, but about 60% of patients with NL are diabetic [2]. This data shows us that even though we mostly

associate NL with diabetes, it can coexist with other diseases such as: thyroiditis, inflammatory bowel disease, sarcoidosis, obesity, dyslipidemia, hypertension, coronary heart disease, stroke, and reduced renal function [1,3]. Skin lesions mostly appear on the anterior parts of lower extremities, but other less frequent locations have been reported, such as the scalp, face, trunk and upper limbs, or genital region [4].

To this day, the pathogenesis of NL remains unclear. Due to its association with diabetes some authors, believe NL could be predominantly linked to microangiopathy. However, this theory would not explain how patients without diabetes develop symptoms of the disease [2]. Additionally, there are studies suggesting that NL lesions show a higher blood flow than in the surrounding skin [5].

It is also very important, when it comes to NL in diabetic patients, that the severity of hyperglycemia and the level of diabetic control have always been questionable. In a case report by Blevanis [2], skin lesions did not improve, despite improvement in glucose control in a diabetic patient, which would confirm that there is no correlation between glycemic control and NL activity..

Another theory suggests that NL can be triggered by immunological mechanisms, in which either an immune complex disease or autoantibodies targeting vessel wall tissue antigens represent the triggering events. Detection of immunoglobulin M, C3, and fibrin in the walls of blood vessels and the dermal-epidermal junction in affected skin seems to support this theory [5].

Abnormal collagen production is another factor potentially related with the pathogenesis of NL. During the course of the disease, a decrease in collagen production and coexisting collagen and elastin degeneration can be observed [2].

Genetic factors are also taken into consideration as being potentially connected with the pathogenesis of NL. This theory remains questionable, as only a few cases of familial NL have been reported. Moreover, several studies have found no genetic involvement in NL, showing no differences in the HLA system between patients with type 1 diabetes with NL and those without NL symptoms [5]. Sometimes NL may also occur as a result of the Koebner phenomenon, i.e. it can develop after minor traumas or surgical procedures [6].

At the beginning, NL presents as asymptomatic, small red-brown papules, and as the disease progresses, the lesions develop into yellow-brown plaques with well-defined borders with central atrophy and telangiectasias. The affected skin is often fragile, resulting in painful ulcerations in up to 30% of patients. It should be considered that in some patients with long-lasting NL, squamous cell carcinoma may develop within the lesions [3,7].

The diagnosis of the NL often can be made based only on clinical examination, but histopathological examination may be necessary to differentiate from other conditions, e.g. granuloma annulare, necrobiotic xanthogranuloma, sarcoidosis, diabetic dermopathy, lipodermatosclerosis, erythema nodosum, morphea and lichen sclerosus [1,8].

Skin biopsies reveal palisaded granulomatous inflammation horizontally layered within degenerated collagen, a disappearance of elastic fibers, and an associated lymphoplasmacytic infiltrate, along with general scarification of the dermis [4,9].

Little is known about the characteristic findings of NL in dermoscopy, but this seems to be a potentially useful non-invasive tool to differentiate NL from other granulomatous skin conditions. In one study, dermoscopic examination revealed linear vessels with branches distributed uniformly on the background of yellow structureless areas. White linear streaks were also visible [10].

Aim of the work

As NL is a disease with a complex, multifactorial etiology emerging as a major therapeutic problem, this review aims to extract, from available literature from the last 5 years, treatment methods with the greatest potential in managing NL, highlighting the most effective ones and those with the least amount of side effects.

Methods

The review of scientific literature included scientific publications available in PubMed, Google Scholar, and ViaMedica. The keywords used for the search were "necrobiosis lipoidica" and "necrobiosis lipoidica diabetorum" in combination with "treatment", "therapeutic methods", "ulceration", "JAK inhibitors". Subsequent searches were extended to include related keywords. Scientific papers written between 2019 and 2024 and published in English were selected from the listed electronic databases. Clinical trials, reviews, systematic reviews, and case reports were included. Papers were excluded if their titles and abstracts did not align with the topic of the review, did not meet the purpose of our article, or were duplicates in the listed electronic databases. Finally, 22 articles were included in the review.

Literature review results

Because of an unclear etiopathogenesis and the rare occurrence of this entity, no uniform therapeutic recommendations have been created. Scientific data regarding treatment for NL consists mostly of case reports and rather small clinical trials.

Topical and intralesional corticosteroids have been the first-line treatment for active, enlarging lesions for years. Even though they reduce symptoms of the disease, data concerning the effectiveness of monotherapy with corticosteroids differs. What is worth noticing is that the longer corticosteroids are used, the greater the chance of skin atrophy development, which increases the risk of ulceration. As an alternative to topical steroids, calcineurin inhibitors and retinoids have been used with unsatisfactory results [1,8]. Different therapies such as systemic corticosteroids, biologic agents, platelet aggregation inhibitors, IVIG, hyperbaric oxygen therapy, cutaneous blood flow modulators, aspirin, dipyridamole and immunomodulators (e.g. cyclosporine, dimethyl-fumarate, or thalidomide) have also been used with various responses [3,6,11]. However, the need for more effective and

targeted treatments continues to push researchers towards further studies in this field.

Light and laser therapies

In the last few years, different light and laser therapies have been used with varying but mostly promising effects (Table 1). MAL-PTD (methyl-aminolaevulinate-based photodynamic therapy) and ALA-PDT (aminolevulinic acid photodynamic therapy) were both mentioned in literature as NL treatment with various outcomes, which shows the need for larger clinical trials to determine the efficacy of these methods [7]. Li Pomi et al. [1] carried out a first cohort study regarding photodynamic therapy (PDT) in NL patients. In their experience, the MAL-PTD-treated group and ALA-PTD-treated group obtained very similar results. In both groups, around 30% of patients achieved complete resolution, while partial improvement was noted in around 60% of cases. What is more, ulcerative NL responded better to PDT therapy. 100% of patients with ulcerative NL showed response to treatment compared to a 75% respond rate in non-ulcerative NL patients [1]. Gutierrez et al. [6] also reported impressive results in a one-year follow-up after pulsed dye laser (PDL) therapy in one patient. There is little scientific data regarding PDL usage for NL management. To use this method on a larger scale, more research which would give us standardized treatment algorithms is required [6]. It is worth paying attention to one of the most frequent side effects of PDT use in NL, which is burning pain especially occurring in ulcerated lesions right at the beginning of the treatment session. The pain quickly becomes intense, reaching its peak in the first few minutes of exposure. Most of the time, the pain decreases with each additional minute of therapy. This is the greatest limiting factor of PDT. Subjective assessment of pain intensity sometimes forces patients to forego treatment [1].

Table 1. Efficacy of different light and laser treatment methods [1,6,7]

Treatment method	Number of patients	Significant improvement	Intermediate improvement	No improvement or deterioration
ALA-PDT	15	6	7	2
MAL-PDT	88	4	54	30
UVA1	14	3	4	7
PUVA	65	17	29	19
CO2 LASER	12	1	11	0
PDL	4	2	2	0

Notes: ALA-PDT – Aminolevulinic acid photodynamic therapy, MAL-PDT – Methyl-aminolevulinate-based photodynamic therapy, UVA1 – Ultraviolet A1, PUVA – Psoralen and Ultraviolet A, PDL – Pulsed dye laser.

In their review, Rajabi-Estarabadi et al. [7] mentioned a few different light and laser treatment methods. PUVA is the most frequently described method for NL management in the review. Some studies regarding PUVA have shown only good results, but in others, poor outcomes have been noted. More standardized studies on PUVA are needed to establish its efficacy as a treatment for NL. They also point out that UVA1 treatments have been tried on patients with NL with various results. Among the different light and laser therapies, a fractional CO2 laser was the least studied modality for NL. There are several cases describing NL patients treated with a fractional CO2 laser with intermediate or significant improvement, but there is still too little data to clearly determine the efficacy of this method [7].

Janus kinase (JAK) inhibitors

There has been an increase in the number of case reports considering JAK inhibitors being used as monotherapy in NL treatment with good results. However, details about the possible role of JAK signaling in NL development remain unknown. We need more scientific data to establish if JAK

inhibitors are a solution in ulcerative and non-ulcerative NL treatment. In a case report by Arnet et al., treatment with JAK 1 inhibitor – abrocitinib turned out to be effective. New lesions did not occur, while the old lesions showed signs of improvement. Even though the outcome had a positive impact on the patient's quality of life, the researchers seemed to expect better results. Moreover, they pointed out that abrocitinib was less effective than the non-selective JAK inhibitor tofacitinib when it came to healing NL. This may suggest that other Janus kinases than JAK1 Janus kinases possibly have an even stronger connection with the pathogenesis of NL. To determine this, more scientific data is needed [12]. Rapid improvement was observed in three patients treated with tofacitinib in the report of McPhie et al. [13]. All three patients after 4 weeks of treatment experienced erythema reduction and flattening of the lesions. One patient had an ulceration that healed completely within four weeks of initiating therapy. We can conclude that tofacitinib can be a beneficial therapeutic option for granulomatous diseases such as NL, including cases of chronic, treatment-resistant ulcerations [13]. In one case report by Erfurt-Berge et al., young woman with a long history of ulcerative, painful, treatment-resistant NL, type 2 diabetes, and obesity was successfully treated with tofacitinib. After 12 weeks of treatment, a significant improvement was observed, including healing of the ulcers, reduction of erythema, and notable pain relief, allowing for the discontinuation of pain medications [14]. In some cases reported on in literature, JAK inhibitors were administered alongside additional treatment methods to further enhance their effectiveness. Damsky et al. [9] described very successful results of treating a patient with recurrent long-lasting NL using tofacitinib and intralesional triamcinolone simultaneously. The researchers assumed that this satisfactory effect could be achieved due to blocking JAK-dependent and JAK-independent pathways at the same time. This suggests that therapy including both a JAK-inhibitor and intralesional corticosteroids is a good choice in the case of recurrent and recalcitrant NL [9]. Janßen et al. [15] presented another case of successfully treated NL which occurred after a minor injury. Using tofacitinib in monotherapy, they achieved an anti-inflammatory effect and noticeable wound healing. To enhance the therapeutic effect, a hair-containing punch graft transplantation was performed. After 5 months, complete wound epithelization

was obtained [15].

Tumor necrosis factor (TNF) inhibitors

Anti-TNF therapies are known to destroy granuloma in granulomatous disorders. Given this, tumor necrosis factor (TNF)- α inhibitors, such as infliximab, etanercept, and adalimumab, are a potentially effective treatment method for NL, as it is believed to be a granulomatous condition. Sandhu et al. [16] described a 74-year-old female with poorly controlled type 2 diabetes with multiple ulcerated NL lesions within the right pretibial area. Treatment with adalimumab administered subcutaneously was introduced, as previous treatments did not bring any improvement. After 28 weeks of adalimumab therapy, there was complete reepithelization of all wounds, with only atrophic scars remaining. In the follow-up, the wounds remained healed for over a year after adalimumab discontinuation [16]. Fertitta et al. [17] presented a case of a man with ulcerative NL of the elbow affecting joint mobility treated successfully with anti-TNF- α . Beforehand, antituberculosis treatment, topical steroids, and hydroxychloroquine were administered with no effect. Due to this, infliximab was introduced. After 2 months, significant improvement was noted in MRI imaging. After 4 months, the patient almost completely regained elbow mobility. Anti-TNF- α drugs should also be considered in the management of NL, as they have shown promising results [17].

Other biological drugs

Other biological drugs have also been used. Successful topical application of aryl hydrocarbon receptor agonist-tapinarof (decrease in TNF- α /IL-23/IL-17 levels and inhibition of STAT-6 activation) have also been reported. Due to its mechanism of action, tapinarof and its topical application may be a promising therapeutic option for NL. As yet, very few studies have been conducted and only individual cases report NL improvement after therapy with tapinarof [5]. What

is more, a monoclonal antibody against IL-17A-secukinumab was used in one case series as a treatment for long-standing, reluctant NL. Three out of four patients enrolled in the study received complete treatment, while the fourth patient withdrew due to a subjective insufficient response to treatment. Two out of three remaining patients did not experience deterioration of lesions, but they did not show significant improvement either. Only the last patient finished study with improvement confirmed through a biopsy. Histologic reduction of lymphohistiocytic inflammatory infiltrate and reduction in collagen degeneration were noted. This study suggests that secukinumab may be a potential treatment for NL, although further research and standardized outcome assessment tools are needed [18].

Doxycycline

Besides its antimicrobial properties, doxycycline is being considered as potential management in NL treatment. Burns [19] reported a case of a 12-year-old girl with NL confirmed by histopathology and poorly controlled diabetes. Intralesional triamcinolone and topical tacrolimus were initially introduced but with minimal unsatisfactory improvement. Additionally, intralesional triamcinolone led to subcutaneous atrophy. Due to poor results, doxycycline monotherapy was started. After 3 months of treatment, there was significant improvement, with resolution of the subcutaneous atrophy [19].

In another case report [2], some wounds improved, and others completely resolved after 4 months of doxycycline treatment. 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 [2].

Although doxycycline is typically used for its antimicrobial properties, it also inhibits matrix metalloproteinases. What is more, doxycycline has been shown to inhibit granuloma formation in vitro. This mechanism could be useful in NL management [2,19].

Skin grafts

Another treatment option mentioned in literature is sequential punch skin grafting. Ulcerated NL epithelialized completely after sequential punch skin grafting in a 31-year-old smoker with NL with no comorbidities. In this case, the lesions had not improved with any topical or systemic treatment. The researchers performed two punch skin grafting sessions in total in order to increase pain control and limit wound progression. Complete epithelialization was achieved 6 weeks after the procedure. Sequential punch skin grafting may be considered as an interesting option for managing hard to heal ulcerative NL lesions, as it is a relatively simple procedure, as well as being affordable from an economical point of view [20]. For people with high demands concerning aesthetic results, some therapeutic options have also appeared. A 30-year-old diabetic woman with a large NL on her leg with very high aesthetic expectations was successfully treated with staged resections of a lesion and reconstruction with a dermal template and full thickness skin grafts. The researchers reported that the results were very satisfying for the patient [21]. An interesting case was presented by Quintana-Castanedo et al. [11]. They used an innovative and effective method on a 28-year-old patient with type 1 diabetes to treat ulcerative NL. The ulcer was initially irrigated with sevoflurane. After sevoflurane irrigation, punch grafting was performed to cover the wound bed. After the procedure, the researchers noted an extremely quick reduction in pain. Only 3 days after the procedure, analgesics were completely stopped. What is more, just 3 weeks after punch grafting, full epithelialization of the ulcer was observed, which is without a doubt a huge success [11].

Pentoxifylline

Pentoxifylline (PTX) was studied by Hrin et al. [22] as a treatment for NL with rather poor effects. 10 patients who were previously treated unsuccessfully with different methods, such as topical corticosteroids and even systemic prednisone therapy, were introduced to PTX therapy. PTX

was well tolerated, but only 4 of the patients achieved disease inactivity. In order to obtain similar results, other patients required additional treatment methods. These results demonstrate that PTX, although carrying a low risk of side effects, is not a highly effective treatment choice, especially when used as monotherapy [22].

Platelet-rich plasma

There is some evidence in literature supporting the use of platelet-rich plasma in NL as an effective treatment method. Naumowicz et al. [5] in their review mentioned very good results from the application of platelet-rich plasma to NL skin lesions in the form of gel. All 15 patients achieved full resolution of any changes in the skin along with no side effects [5].

Compression therapy

Lastly, compression therapy is also noted to bring benefits to some patients during NL therapy. This may support one of the theories regarding the etiopathogenesis of NL which states that in addition to collagen degeneration and immune-complex deposition, there is a prominent vascular component with NL [8].

Conclusions

NL is a rare entity causing many clinical difficulties. Firstly, further multicenter studies on elucidating the etiopathogenesis of NL are needed to understand the mechanisms leading to the development of this disease. Secondly, there are no standardized tools or scales that would help with therapy outcome assessment. Creating such tools is crucial, as the assessment of therapeutic success is mainly subjective, which may result in inconsistent outcomes throughout various medical centers.

Thirdly, even though no single therapy method is clearly superior to another, two seem to stand out. Therapies involving light are emerging as a potentially effective treatment option with the least risk of side effects. With this paper, we would like to draw researchers' attention to light therapies. PDT seems to be an especially safe modality with minimal side effects, as well as having large potential even in healing ulcerated NL lesions. Another group of medications attracting our attention are JAK inhibitors. In a few case reports, JAK inhibitors were responsible for significant improvement and have shown promising results when used in a monotherapy, as well as in an element of complex therapy. Despite good treatment results, more high-quality research is needed to prove the effectiveness of JAK inhibitors in NL treatment.

In conclusion, further randomized studies on larger groups of patients are required to establish real efficacy and the safety of each method and create uniform therapeutic guidelines for NL treatment.

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