

DISSEMINATED GRANULOMA ANNULARE ASSOCIATED WITH NECROBIOSIS LIPOIDICA – CASE STUDY

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Abstract

Keywords:

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Granuloma annulare and necrobiosis lipoidica are granulomatous diseases with an unclear etiology. The presence of both pathologies in the same patient is quite rarely reported.

Clinical case: We present a 75-year-old patient, from urban environment, with disseminated granuloma annulare and necrobiosis lipoidica, and we aim to point out the clinical progress as well as the histopathological and therapeutic aspects of both diseases. After paraclinical investigations, the patient was also diagnosed with diabetes mellitus.

The recommended treatment was Ofloxacin 400 mg/day, Doxycycline 100 mg/day and Rifampicin 150 mg (2 cps. every 12 h) for three consecutive days/month over a period of four months, and 0.1% Tacrolimus (one application/day in the evening).

The 4-month evolution since the beginning of the treatment has been favorable only for the granuloma annulare lesions.

Discussions: Granuloma annulare and necrobiosis lipoidica can be associated with diabetes mellitus and more frequently affect women. The concurrent occurrence of both diseases has been rarely reported, only 11 cases presenting this association.

There is no standard treatment for the two diseases. The favorable result of the therapy using cyclins is due to the anti-infectious, anti-inflammatory and immunomodulatory actions of these agents.

Conclusion: The association of the two diseases is very rare and we require further investigations to elucidate common pathogenic mechanisms and establish optimal therapy.

Introduction

Granuloma annulare (GA) and necrobiosis lipoidica (NL) are granulomatous diseases with an unclear etiology. The presence of both pathologies in the same patient is quite rarely reported.

Granuloma annulare is a benign chronic inflammatory dermatosis whose clinical and histological aspect (palisade granuloma) is characteristic. It

was described for the first time in 1895 by Thomas Colcott Fox (1), but the paternity of the name "granuloma annulare" belongs to Henry Radcliffe Crocker (1902) (2). Granuloma annulare has several clinical subtypes: localized, generalized, subcutaneous, perforating and rarely macular or plaque, palmar or pustular. Some authors consider actinic granuloma as a subtype of granuloma annulare,

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while others consider it a different category of disease.

Granuloma annulare may occur in all age groups with a lower frequency in childhood (3, 4). Only 11 cases associating GA and NL have been described in the published literature. Nine of those patients were women (82%), with a mean age of 30 years old when the two diseases were diagnosed. Men (two out of 11 patients, 18%) had a mean age of 25 years old when diagnosed. Necrobiosis lipoidica lesions were present on the inferior limbs, and GA lesions were noted in the ankles, legs, trunk and upper limbs. From all those 11 patients, 7 (64%) have had diabetes or were pre-diabetic (5). Another study claims that the association of the two diseases was unrelated to diabetes (6).

We present a patient with disseminated GA and NL, and we aim to point out the clinical evolution as well as the histopathological and therapeutic aspects of both diseases.

Clinical case

A 75-year-old patient, from urban environment, requested dermatological consultation for multiple lesions with arciform outline, with dimensions between 0.3–5 cm, discreet edges, erythematous and pale center, disseminated on the upper limbs (Figures 1 and 2) and for hyperpigmented plaques and placards with polycyclic contour, slightly atrophic center, yellowish and fine squamous surface, symmetrically arranged on the legs and the dorsal feet (Fig. 3).

Historically, we note that lesions occurred concurrently, one year prior to hospitalization, and



Figure 1. Lesions with arciform outline, with dimensions between 0.3–5 cm, discreet edges, erythematous and pale center



Figure 2. Lesions with arciform outline, discreet edges, erythematous and pale center



Figure 3. Plates and placards with polycyclic contour, hyperpigmented, slightly atrophic center, yellowish and fine squamous surface, symmetrically

over time they increased in number and size. The patient did not follow any outpatient treatment.

Paraclinical investigations revealed high serum glucose (160 mg/dL), the patient being diagnosed with diabetes mellitus.

The histopathological examination confirmed the clinical diagnosis of GA, highlighting the presence of histiocytic granulomas containing rare multinucleated cells disposed in the superficial and middle dermis, degenerated collagen strips in their vicinity and perivascular lymphocytic infiltration. There were no cases of mucinous areas (Figures 4 and 5).

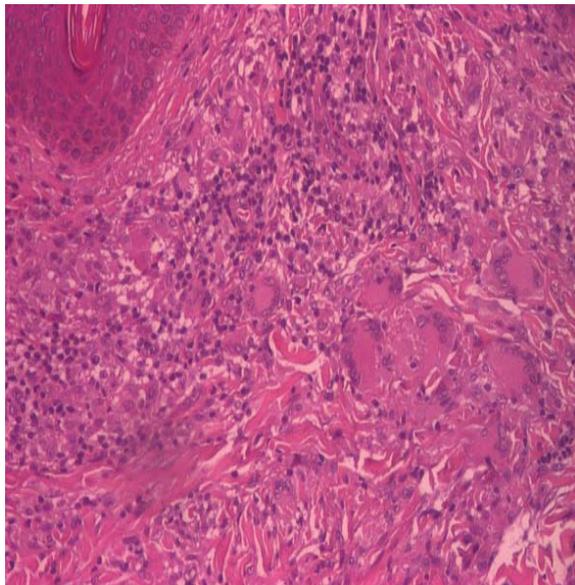


Figure 4. Histiocytic granulomas containing multinucleated cells in the superficial and middle dermis, HE stain, x100

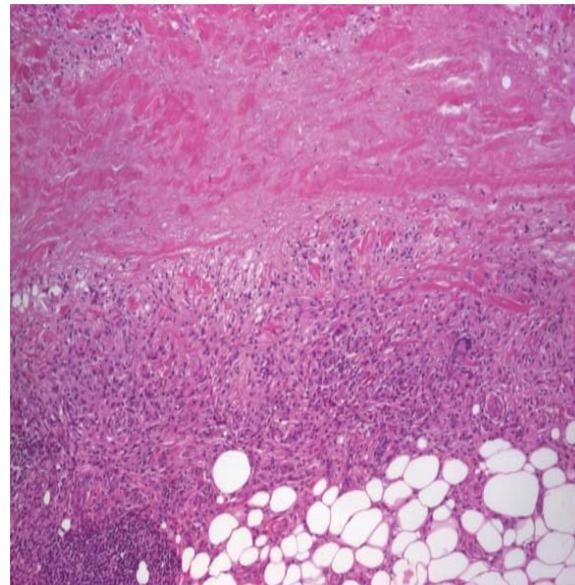


Figure 6. Granulomas containing epithelioid cells, histiocytes and multinucleated Langhans giant cells, interesting deep dermis and hypodermis, HE stain, x40

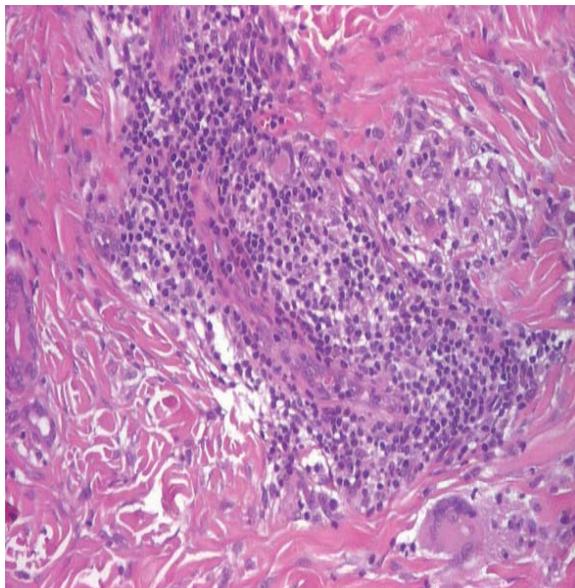


Figure 5. Degenerated collagen strips and perivascular lymphocytic infiltration, HE stain, x100

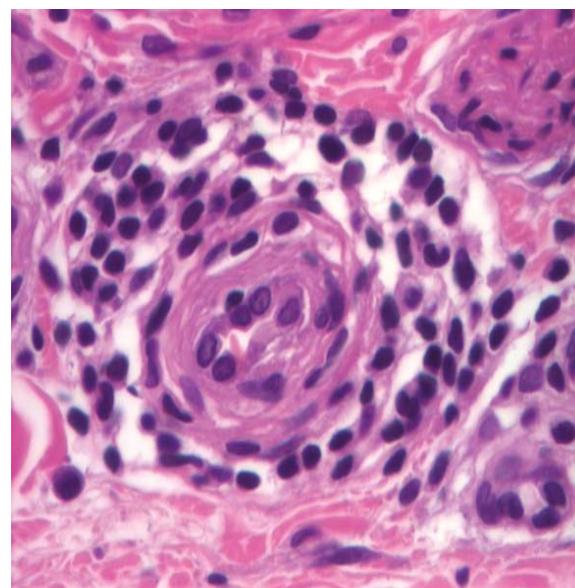


Figure 7. The blood vessels of the dermis have a thickened wall and perivascular lympho-plasmocytic inflammatory infiltration, HE, x200

In the case of clinically diagnosed lesions as NL, histopathological examination reveals characteristic changes: the skin presents an atrophic epidermis, areas of chronic granulomatous inflammation containing epithelioid cells, histiocytes and giant multinucleated Langhans cells in the deep dermis and hypoderm (Fig. 6). In the blood vessels of the dermis there is a vasculitic process: they have a thickened, hypertrophied wall and a diminished lumen, being surrounded by an inflammatory lymphocytes and plasma cells infiltrate (Fig. 7).

The histopathological examination was performed on the basis of two cutaneous fragments taken from a lesion located on the anterior face of the right forearm and the dorsal face of the right foot.

The recommended treatment was Ofloxacin 400 mg/day, Doxycycline 100 mg/day and Rifampicin 150 mg (two cps. every 12 h) for three consecutive days/month for four months, and 0.1% Tacrolimus (one application/day in the evening).

The 4-month evolution since the beginning of the treatment has been favorable only for the GA lesions.

Discussions

Disseminated granuloma annulare (DGA) represents 2.8-15% of all GA cases, occurs predominantly in adults, predominates in women (sex/ratio of 6/1) and is characterized by the presence of at least 10 cutaneous lesions or plaques. The trunk is frequently involved, but other topographical regions such as the neck, limbs, face, scalp, palms and soles may also be involved (4, 7).

The *etiopathogeny* of annular granuloma is not elucidated, and there are several pathogenic hypotheses: microangiopathy, immunological vasculitis, delayed hypersensitivity reaction, neutrophil migration defect with abnormal neutrophil accumulation, and elevated serum β -glucuronidase degradation implicated in mucopolysaccharide degradation (3, 8).

Diseases associated with GA are diabetes mellitus (9), dyslipidemia (10), thyroid disorders (auto-immune thyroiditis) (11) and malignancies (Hodgkin's lymphoma, pulmonary adenocarcinoma, breast carcinoma, ovarian neoplasm) (12); DGA is associated with metabolic disorders in 60-75% of cases (3, 4, 13).

There have been reports of drug-induced cases (allopurinol, diclofenac, quinidine, calcitonin, ACE inhibitor and calcium channel blockers, etc.) (3, 4), viral infections caused by HIV (14), Epstein-Barr, hepatitis B and C viruses (15, 16), herpes zoster virus (17), *Koch bacillus* infection (18, 19), and after vaccination for hepatitis B or after insect bites, trauma or sun exposure (20).

Genetic predisposition is argued by familial cases of GA in twins or brothers of several generations. The HLA-B8 frequency was increased in some cases of localized GA, while HLA-A29 and HLA-BW35 were reported to be elevated in DGA (4).

In our case, the *differential diagnosis* of DGA was done with sarcoidosis, lipid necrosis, interstitial granulomatous dermatitis, subacute erythematous lupus, lichen planus, and fungoides granulomatous mycoses.

The *evolution* of DGA is chronic, responds poorly to treatment, and relapses frequently.

DGA treatment is not standardized. Some authors (21) reported good results after 3-5 months of treatment with Rifampicin 600 mg, Ofloxacin 400 mg and Minocycline hydrochloride 100 mg one day a month.

Favorable results were also published after the administration of other antibiotics such as Cefaclor, Cefixim, Penicillin, Amoxicillin, Ciprofloxacin, Erythromycin, Clarithromycin and Trimethoprim-sulfamethoxazole (22).

Other alternatives are dermatocorticoids; calcineurin inhibitors (tacrolimus or pimecrolimus) (23); general corticosteroid therapy; antipaludial synthesis; retinoids; cyclosporine; dapsone; infliximab; phototherapy (PUVA, UVB) (2); photodynamic therapy (24).

Necrobiosis lipidica is a chronic granulomatous disease characterized by erythematous papules or centrifugally developing plaques, becoming yellowish-brown, with central atrophy. It was first described in 1929, in patients with diabetes, by Opensheim, who called it "diabetic lipid atrophic dermatitis". In 1932, Urbach renamed it diabetic lipid necrobiosis. The term necrobiosis refers to the degeneration of collagen, and the lipid means the extracellular accumulation of lipids (3).

In 1935, Goldsmith reported the first case of NL in a non-diabetic patient. Meischer and Leder (in 1948) and Rollins and Winkelmann (in 1960) described the condition in several non-diabetic patients, which led to the renunciation of the term "diabetic" (25).

Necrobiosis lipidica is found in 0.3-1.2% of diabetic patients and it is rare in children with diabetes (0.006%). It is more common in patients with type 1 diabetes. The onset is in the third decade of life in diabetic patients and in the fourth decade in non-diabetics, with women being more frequently affected than men (26). In 60% of patients, diabetes precedes the onset of lipid necrobiosis, while 25% of patients have had lesions that occurred with concomitant diabetes. In 15% of patients, NL precedes the onset of diabetes.

Etiopathogenesis is uncertain, with several hypotheses being issued.

Due to the strong relationship between diabetes and NL, many studies have focused on diabetic microangiopathy. Diabetic changes of the kidney and eye vasculature are similar to the vascular changes observed in NL. A glycoprotein deposition in the walls of the blood vessels may be the cause of diabetic microangiopathy. A similar glycoprotein deposition is also found in NL.

Another theory is based on the deposition of immunoglobulins and fibrinogen in blood vessel walls in patients with NL. The antibody-mediated vasculitis can initiate changes in blood vessels, with the subsequent appearance of necrobiosis. Immune complex deposition, together with platelet aggregation and clotting appears to play a role in the etiopathogeny of this disease.

An additional etiological theory focuses on modified collagen in NL. Denatured collagen fibers are the cause of diabetic organ changes and accelerated aging. Higher levels of lysyl oxidase in people with diabetes are responsible for increased cross-linking between collagen fibers, which explains the thickening of the basal membrane in NL.

Changes due to trauma may also be involved (cases of necrotizing postoperative scars have been reported, Köebner phenomenon may be present in NL), inflammatory and metabolic changes. In this context, migration of neutrophils leading to an increased number of macrophages could be involved, which would explain the formation of granuloma in NL.

The abnormality of glucose transport by fibroblasts in people with NL has also been discussed.

Clinically, oval or irregular plaques appear, with yellowish, telangiectatic atrophic center and a purple violet, convex periphery. By confluence they can make polycyclic posters. Election location is pretibial, usually bilateral. In 15% of cases, the lesions are present in other topographical regions (hands, forearms, face, scalp). Occasionally, NL lesions can appear on the thighs, popliteal regions and on the legs. Gradually, they become depressed, almost atrophic and entirely brown plaques. The accumulation of lipids may be observed in the center of the lesion through the transparency of the epidermis. Scales may remain fine or they may become more prominent when ulceration is imminent. The lesions are usually painless as a consequence of nerve damage in the skin. There are also rare cases of perforating NL. This form is always associated with diabetes (3). Lesions can spontaneously regress, become chronic, or can ulcerate. Painful ulceration occurs in about 15% of cases.

Paraclinical investigations are not indispensable for NL diagnosis. The patient will be evaluated to detect the presence of diabetes.

Histopathologically, interstitial and palisadic granulomas occur in subcutaneous tissue and dermis. The lymphocytic composition of the dermal infiltrate is mainly composed of T cells (T-helper cells). Granulomas (made up of histiocytes, multinucleated cells, lymphocytes, plasma cells and eosinophils) are mixed with collagen degeneration areas (26).

Practically, the histopathological examination reveals thinning of the dermis, dermal obliteration by granulomatous infiltrate and sclerosis, extracellular deposits of lipids in the superficial dermis and reduction of the number of intradermal nerves (3).

Direct immunofluorescence has demonstrated the presence of IgM, IgA, C3 and fibrinogen in the blood vessels, causing thickening of the vascular walls. In non-diabetic subjects, vascular changes are not so pronounced.

Differential diagnosis of NL lesions in our case was made with with ringleaf granuloma, necrobiotic xanthogranuloma and sarcoidosis.

The histopathological difference between GA and NL is difficult. GA is usually located in the superficial and medial dermis, while NL affects the entire dermis and subcutaneous tissue. The GA model is focal and palisadic, while in NL it is dif-

fuse, with horizontal collagen degeneration. Mucin is present in GA, while extracellular lipid deposits are present in NL (27)

The evolution of NL is usually chronic, with slow progression and eventual stabilization over the years. Spontaneous resolution has been encountered in some cases. Possible complications include ulceration, infection and squamous carcinoma development (rarely). The presence or progression of NL is not correlated with glycemic control.

There is no consensus on NL treatment. The combination of aspirin and dipyridamole was proposed as a treatment, but some studies concluded that a combination of 300 mg aspirin and 75 mg dipyridamole, three times a day for eight weeks, does not confer any benefit (28). The efficacy of pentoxifylline was reported in NL when used at a dose of 400 mg three times a day for at least six months (29, 30). Prostaglandin E1 has been used as a treatment in a young non-diabetic woman, improving the appearance of NL (31). Intra-nasal triamcinolone has been reported to be effective in some cases of NL (32).

Ciclosporin used for ulcerative lesions in NL has led to the healing of ulcers without immediate relapse but with a questionable benefit for the rest of the lesions. Ciclosporin inhibits the production of interleukin 2 by T-helper cells, preventing the proliferation of clonal T cells and thereby suppressing immune response to NL.

Mycophenolate mofetil has a strong cytostatic effect on lymphocytes and has also been used to accelerate the healing of ulcerated NL in a non-diabetic patient.

In a case with ulcerative lipid necrosis, the authors achieved healing after administration of Doxycycline (2x 100 mg/day for one month, then 100 mg/day for three months). The favorable outcome is due to the anti-infectious, anti-inflammatory and immunomodulatory actions of Doxycycline (33).

Other tested treatments were Infliximab, Etanercept, Talidomide, Chloroquin, Nicotinamide, Clofazimin, Granulocyte-macrophage colony stimulating factor, Tretinoin, Tacrolimus topic, topical benzoyl peroxide, PUVA (a concern about phototherapy is whether it increases the risk of Squamous cell carcinoma), photodynamic therapy and fractional CO₂ laser therapy.

In some cases, it was recommended to carry out the excision to the deep fascia or peritoneum, followed by skin grafts to cover the defect (6, 7, 8, 9, 26).

DGA and **NL** may be associated with diabetes and affect women more frequently. The concomitant occurrence of the two diseases was very rarely described.

In 1934, Ketron suggested that NL might be a variant of GA based on histological findings. In a

publication in 1941, Francis Ellis suggested that lesions of GA and NL might be the same entity. Ellis mentions the first patient with both diseases in a Wood and Beerman manuscript (34, 35). In 1968, Fred Feldman presented the association of GA and NL in another patient (36). However, researchers' contribution is needed to elucidate common points on the etiopathogenicity of the two diseases.

The evolution of GA and NL is chronic, with poor response to treatment and frequent recurrence. Common treatment includes systemic and topical corticosteroids or intralesional triamcinolone.

Conclusion

The association of the two diseases is very rare and further studies are needed to elucidate com-

mon pathogenic mechanisms and to establish optimal therapy.

Conflicts of interest: none declared.

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Patient consent obtained.

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Bibliography

- Colcott-Fox T. Ringed eruptions of the fingers. *Br J Dermatol* 1895;7:91-95.
- Radcliff-Crocker H. Granuloma annulare. *Br J Dermatol* 1902;14:1-9.
- Pătrașcu V. *Boli dermatologice și infecții sexual transmissibile*, Editura Sitech, Craiova, ed. a III-a, 2014, pag. 573.
- Pătrașcu V, Bocîrnea Alexandra Georgiana, Ciurea ME, Ciurea Raluca Niculina. Disseminated granuloma annulare: 3 clinical cases granulom inelar diseminat: 3 cazuri clinice. *RoJCED* 2015;2:122-127.
- Rupley Katherine A, Riahi RR, O'Boyle Hooper Deirdre. Granuloma annulare and necrobiosis lipoidica with sequential occurrence in a patient: report and review of literature. *Dermatol Pract Concept* 2015;1:29-34. Published online 2015 Jan 30. doi: 10.5826/dpc.0501a03. PMID: PMC4325686
- de Souza Fernanda Homem de Mello, Ferrari Ribeiro Camila, Pereira Marcela Abou Chami, Mesquita Lismary, Lincoln F. Simultaneous occurrence of ulcerated necrobiosis lipoidica and granuloma annulare in a patient - case report. *Anais Brasileiros de Dermatologia*. Print version ISSN 0365-0596 *An Bras Dermatol* vol. 86, no. 5, Rio de Janeiro Sept./Oct. 2011. <http://dx.doi.org/10.1590/S0365-05962011000500023>
- Thornsberry Laura A, English JC III. Etiology, Diagnosis, and Therapeutic Management of Granuloma Annulare. *Am J Clin Dermatol* 2013;4:279-290.
- Goldsmith LA, Katz SI, Gilchrist BA, Paller AS, Leffell DJ, Wolff W. Fitzpatrick's *Dermatology in General Medicine*, Eighth Edition, 2012;44:467-472.
- Nebesio CL, Lewis C, Chuang TY. Lack of an association between granuloma annulare and type 2 diabetes mellitus. *Br J Dermatol* 2002;1:122-124.
- Wu W, Robinson-Bostom L, Kokkotou E, et al. Dyslipidemia in granuloma annulare. *Arch Dermatol* 2012;10:1131-1136.
- Maschio M, Marigliano M, Sabbion A, et al. A rare case of granuloma annulare in a 5-year-old child with type 1 diabetes and autoimmune thyroiditis. *Am J Dermatopathol* 2013;3:385-387.
- Li A, Hogan DJ, Sanusi ID, Smoller BR. Granuloma annulare and malignant neoplasms. *Am J Dermatopathol* 2003;2:113-116.
- Radu-Carlaont Alexandra, Pătrașcu Virgil. Disseminated Granuloma Annulare. Case Presentation. *Dermatovenerol (Buc.)* 2015;60:255-262.
- Toro JR, Chu P, Yen TS. Granuloma annulare and human immunodeficiency virus infection. *Arch Dermatol* 1999;11:1341-1346.
- Ma H, Zhu W, Yue X. Generalized granuloma annulare associated with chronic hepatitis B virus infection. *J Eur Acad Dermatol Venereol* 2006;2:186-189.
- Granel B, Serratrice J, Rey J, et al. Chronic hepatitis C virus infection associated with a generalized granuloma annulare. *J Am Acad Dermatol* 2000;43(5 pt 2):918-919.
- Ohata C, Shirabe H, Takagie K, et al. Granuloma annulare in herpes zoster scars. *J Dermatol*. 2000;3:166-169.
- Kakurai M, Kiyosawa T, Ohtsuki M, et al. Multiple lesions of granuloma annulare following BCG vaccination: case report and review of the literature. *Int J Dermatol* 2001;9:579-581.
- Houcke-Bruge C, Delaporte E, Cateau B, et al. Granuloma annulare following BCG vaccination. *Ann Dermatol Venereol* 2001;4:541-544.
- Andreu-Barasoain M, Gomez de la Fuente E, Pinedo F, et al. Long lasting interstitial generalized granuloma annulare on sun-exposed areas. *Photodermatol Photoimmunol Photomed* 2012;4:216-218.
- Marcus DV, Mahmoud BH, Hamzavi IH. Granuloma annulare treated with rifampicin, ofloxacin, and minocycline combination therapy. *Arch Dermatol* 2009;7:787-789.
- Shilpa Garg, Sukriti Baveja. Generalized Granuloma Annulare Treated with Monthly Rifampicin, Ofloxacin, and Minocycline Combination Therapy. *Indian J Dermatol* 2013;3:197-199.
- Lopez-Navarro N, Castillo R, Gallardo M, et al. Successful treatment of perforating granuloma annulare with 0.1% tacrolimus ointment. *J Dermatolog Treat* 2008;6:376-377.
- Kim YJ, Kang HY, Lee ES, et al. Successful treatment of granuloma annulare with topical 5-aminolevulinic acid photodynamic therapy. *J Dermatol* 2006;9:642-643
- Sunil Kumar Kota, Sruti Jammula, Siva Krishna Kota, Lalit Kumar Meher, Kirtikumar D. Modi. Necrobiosis lipoidica diabetorum: A case-based review of literature. *Indian J Endocrinol Metab* 2012;4:614-620. doi:10.4103/2230-8210.98023 PMID: PMC3401767.
- Pătrașcu V, Giurcă C, Ciurea RN, Georgescu CC, Ciurea ME. Ulcerated necrobiosis lipoidica to a teenager with diabetes mellitus and obesity. *Rom J Morphol Embryol* 2014;1:171-176.
- Scaramuzza A, Macedoni Maddalena, Tadini GL, De Angelis Laura, Redaelli Francesca, Gazzarri Alessandra, Comaschi Valentina, et al. Necrobiosis Lipoidica Diabetorum. *Case Rep Pediatr* 2012;2012:152602. Published online 2012 Apr 22. doi: 0.1155/2012/152602 PMID: PMC3350198
- Statham B, Finlay AY, Marks R. A randomised double blind comparison of an aspirin dipyridamole combination versus a placebo in the treatment of necrobiosis lipoidica. *Acta Derm Venereol* 1981;61:270-271.
- Littler CM, Tschen EH. Pentoxifylline for necrobiosis lipoidica diabetorum. *J Am Acad Dermatol* 1987;17:314-316.
- Basaria S, Braga-Basaria M. Necrobiosis lipoidica diabetorum: Response to pentoxifylline. *J Endocrinol Invest* 2003;26:1037-1040.
- Kuwert C, Abeck D, Steinkraus V, Jakob T, Ring J. Prostaglandin E1 improves necrobiosis lipoidica. *Acta Derm Venereol* 1995;75:319-320.
- Sparrow G, Abell E. Granuloma annulare and necrobiosis lipoidica treated by jet injector. *Br J Dermatol* 1975;93:85-89.
- Mahe E, Zimmermann U. Efficacité de la doxycycline dans un cas de nécrobiose lipoidique ulcérée. *Ann Dermatol Venereol* 2011;10:686-689.
- Ellis FA. Necrobiosis lipoidica: A form of granuloma annulare? *Arch Derm Syphilol* 1941;5:822-828.
- Wood MG, Beerman H. Necrobiosis lipoidica, granuloma annulare, and rheumatoid nodule. *J Invest Dermatol* 1960;34:139-147.
- Feldman FF. Granuloma annulare and necrobiosis lipoidica in the same patient. *Arch Dermatol* 1968;6:677-678.