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Granuloma annulare and necrobiosis lipoidica with sequential occurrence in a patient: report and review of literature

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ABSTRACT Granuloma annulare (GA) and necrobiosis lipoidica (NL) are granulomatous diseases of undetermined etiology. Rarely, both dermatoses have been reported to occur concomitantly in patients. GA and NL are characterized histologically by areas of necrobiosis of collagen. The two diseases share some common characteristics, which may suggest that these dermatoses could occur as a spectrum in some patients or possibly share a similar pathogenesis. We report on a 67-year-old Caucasian woman with a history of NL on the anterior shins that later developed lesions of GA on the breasts, trunk, and wrist. We also review the literature and discuss the characteristics of patients with concomitant GA and NL.

Introduction

Granuloma annulare (GA) is a common idiopathic disorder affecting the dermis and subcutaneous tissues [1]. This benign dermatosis generally presents with generalized or localized lesions; macular, patch, perforating, and subcutaneous GA have also been described [1,2]. The localized form consists of one or more annular lesions composed of dermal papules. The generalized form is less frequently seen, presenting as a generalized papular eruption. Ulceration, while not a typical feature associated with GA, has been seen in the less common perforating variant [2].

Necrobiosis lipoidica (NL) is a rare chronic granulomatous disease characterized by erythematous papules or plaques that grow centrifugally, becoming brownish-yellow with central atrophy [3]. The lesions are typically seen in the pretibial region, but can also appear on the face, penis, scalp, and trunk. Ulceration has been demonstrated to occur in up to 35% of patients with NL [4].

GA and NL differ in their clinical appearance, course, and prognosis. Both dermatoses remain unclear in their pathogenesis. Delayed-type hypersensitivity has been postulated to cause GA [5-8]; other authors mention vasculitis as a potential mechanism [3,9,10]. Microangiopathy has been

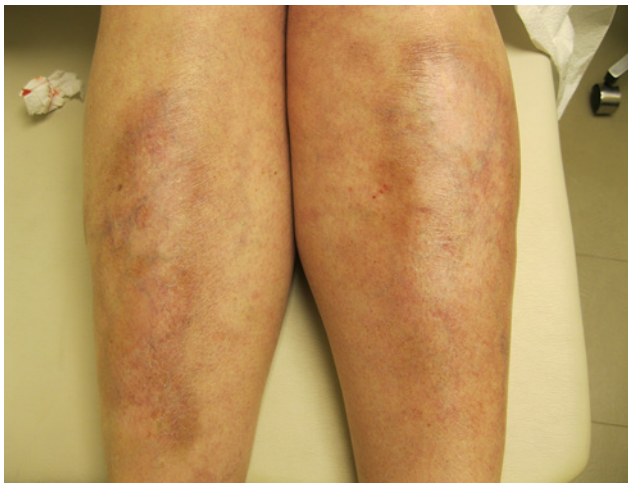

Figure 1. Lower legs with irregular, annular plaques with erythematous rim and yellow, atrophic centers. (Copyright: ©2015 Rupley et al.)

suggested to play a role in the etiology and pathogenesis of NL [4,11,12]. While differences exist, both dermatoses share similarities including an association with diabetes, similar histological patterns, and they more commonly affecting women [1,2,9]. Rarely, patients may present with or subsequently develop both GA and NL [2,3,9,13-18].

To our knowledge, there are ten previously documented cases of GA and NL occurring in the same patient [2,3,9,13-18]. We report on a 67-year-old Caucasian female with a history of NL on the lower legs who presented with erythematous papules and plaques over her breasts, trunk, and wrists; subsequent biopsy of a lesion on the trunk was consistent with GA. We describe the characteristics of patients with concomitant GA and NL and discuss similarities and differences between the two dermatoses.

Case report

A 67-year-old Caucasian woman with a past medical history of diabetes mellitus type 2 and hypertension presented to clinic with a 15-year history of a progressively enlarging, asymptomatic plaques on her lower shins. The patient states the lesions initially began as red bumps that spread out and enlarged. She was seen by an outside dermatologist who had biopsied the area and was told she had necrobiosis lipoidica diabeticorum. She had tried superpotent topical steroids and intralesional Kenalog with moderate improvement.

Physical examination demonstrated erythematous annular plaques with an erythematous rim and atrophic center with yellow discoloration over the lower extremities bilaterally (Figure 1). The patient was treated with intralesional Kenalog with significant improvement.

The patient was seen for follow-up and stated she began developing new lesions on her thighs, trunk upper arm, and wrists (Figure 2A, B, C, D). The lesions appeared as erythematous papules brown plaques, some with a central clearing. Punch biopsy of the chest was performed and revealed discrete areas of palisading histiocytes surrounding collections of mucin with perivascular lymphocytes, suggestive of interstitial granuloma annulare (Figure 3A, B, C).

Discussion

Granuloma annulare is characterized by grouped papules coalescing into annular plaques occurring most commonly on the back of hands and feet. NL typically presents with erythematous papules and plaques that expand centrifugally and tend to occur on the lower extremities. Both dermatoses are more common in women [3].

A PubMed search was performed to find cases of GA and NL occurring in the same patient. The keywords concomitant, granuloma annulare, necrobiosis lipoidica, patient, same, sequential, and simultaneous were used. To the best of our knowledge, there have been 10 reported cases with GA and NL occurring in the same patient. These patients as well as our patient are described (Table 1) [2,3,9,13-18]. Nine of the 11 patients were women (82%) with an average age of 30 years at the time of having both GA and NL. Men (2 of the 11

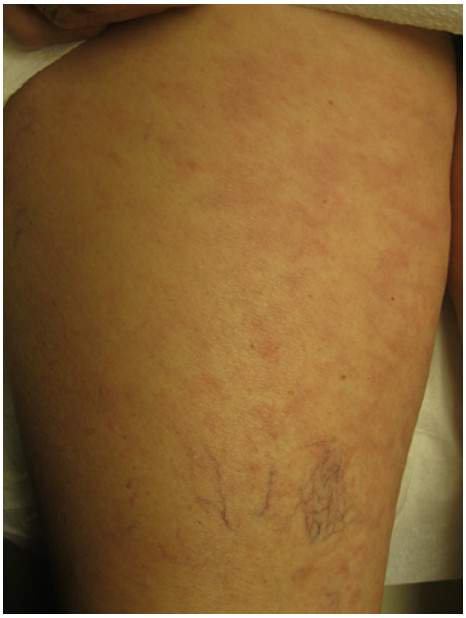

Figure 2A. Left thigh with numerous erythematous papules and plaques. (Copyright: ©2015 Rupley et al.)

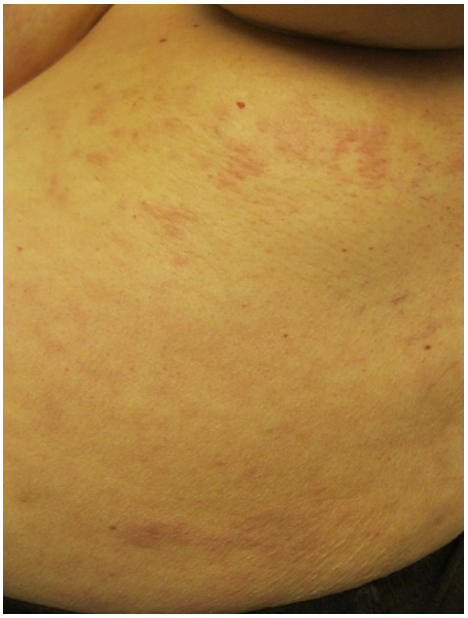

Figure 2B. Lower chest and abdomen with erythematous, indurated papules. (Copyright: ©2015 Rupley et al.)

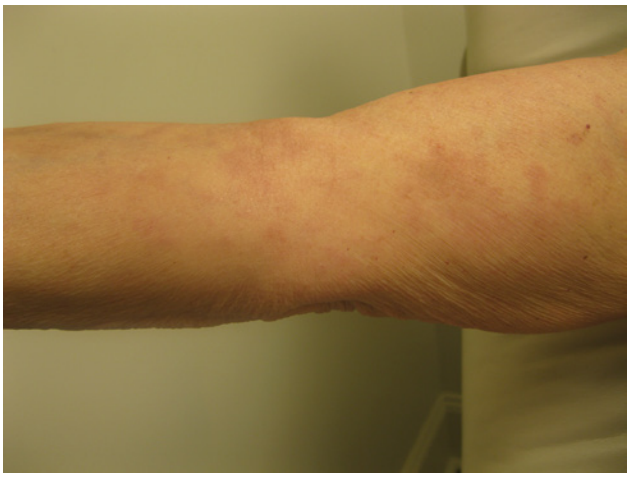

Figure 2C. Right upper extremity with erythematous plaques and annular plaques. (Copyright: ©2015 Rupley et al.)

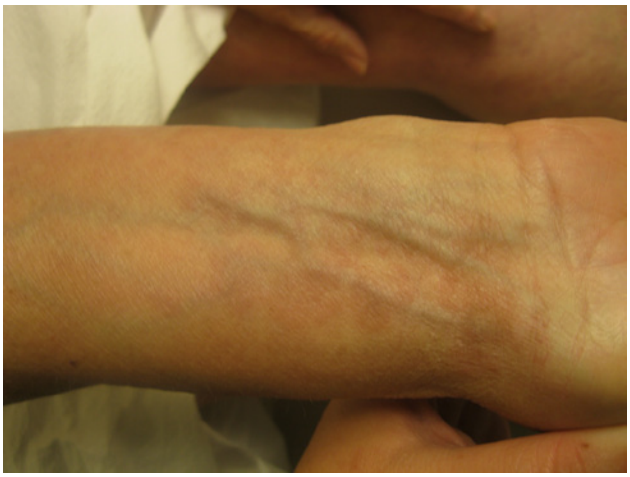

Figure 2D. Right wrist with erythematous and brown indurated papules. (Copyright: ©2015 Rupley et al.)

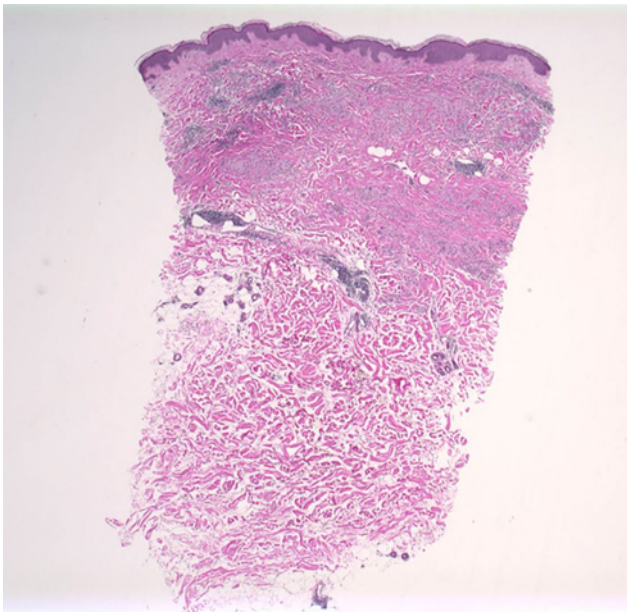

Figure 3A. Scanning view reveals necrobiotic collagen and dermal inflammation. (Copyright: ©2015 Rupley et al.)

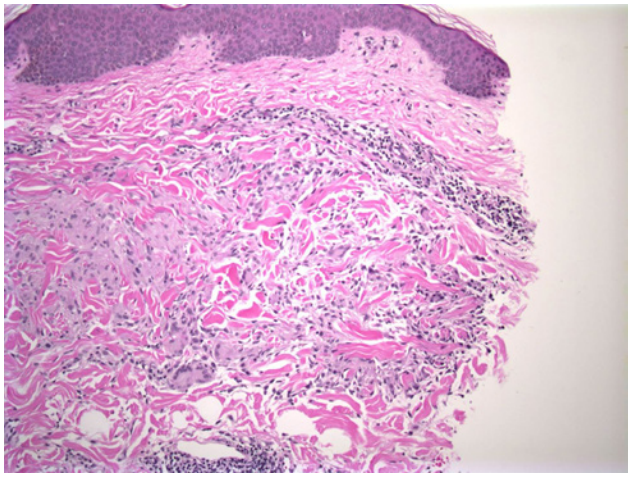

Figure 3B. Individual collagen fibers are swollen and intensely eosinophilic. Histiocytic infiltrate around collagen fibers and a circumferential lymphocytic infiltrate are apparent (40x). (Copyright: ©2015 Rupley et al.)

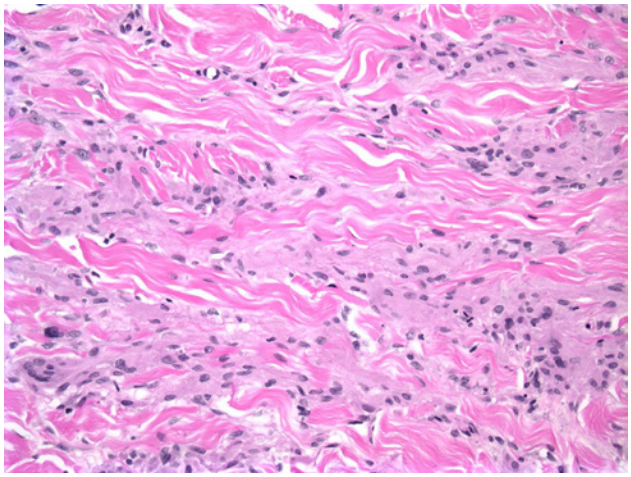

Figure 3C. There is a heavy histiocytic infiltrate surrounding and separating collagen fibers (100x). (Copyright: ©2015 Rupley et al.)

patients, 18%) were of an average age of 25 years when concomitant GA and NL was discovered. Duration of the lesions ranged from 6 months to 20 years. The lesions of NL were all found on the lower extremities [4]. The lesions of GA were found on the ankles, feet, legs, trunk, and upper extremities. Of the 11 patients, 7 patients (7 of the 11, 64%) had diabetes or were pre-diabetic [2,3,9,13-18].

GA and NL share similarities and differences (Table 2) [1-11,13-24]. Both diseases can present with annular lesions and rarely involve the face. Both also occur more frequently in women. Histologic examination of both GA and NL can demonstrate central areas of necrobiosis with an infiltrate of histiocytes and lymphocytes [13]. The infiltrate may also contain epithelioid cells and giant cells [13]. Granuloma annulare has increased mucin in the centers of the granulomas, while NL shows increased extracellular lipids [3]. GA has been

TABLE 1. Cases of concomitant granuloma annulare and necrobiosis lipoidica in the same patient [2,3,9,13-18]. (Copyright: ©2015 Rupley et al.)

Case	Age / Race Sex / DM status	Duration of Having Both GA and NL	Clinical Appearance	Ref
1	25/C/F/ND	5 years	NL: firm, yellow shiny plaque with telangiectasias on pretibial region of the right leg GA: irregularly shaped annular lesions on volar right wrist	[13]
2	30/NR/F/DM2	NR	NL: large superficial oval lesion on shins GA: skin colored papules in an annular pattern on dorsal left foot	[15]
3	31/NR/F/DM2	NR	NL: bilateral pretibial plaques with atrophy GA: red-brown papules on the dorsal feet	[14]
4	23/NR/F/ND	NR	NL: discreet reddish-brown patches with a yellow hue on the left pretibial surface GA: well-defined erythematous annular lesion with central clearing on right lower leg	[16]
5	57/C/F/ND	20 year	NL: irregular oval plaques on bilateral pretibial regions GA: annular erythematous nodules on feet, thighs, back, arms, hands	[9]
6	70/C/F/DM2	6 months	NL: ulceration of bilateral lower extremity including the pretibial region GA: widespread papular and annular eruption	[2]
7	10/C/F/MODY	2 years	NL: erythematous plaques with waxy central clearing on left pretibial region GA: dyschromic red-brown plaques on the bilateral ankles	[17]
8	39/NR/M/ND	3 years	NL: brownish yellow confluent plaques with atrophic centers on ankles GA: violaceous annular plaques on upper limbs, thighs and abdomen, with infiltrated and defined borders	[3]
9	11/C/M/DM1	1.5 years	NL: large brown plaque with an atrophic center on pretibial region GA: pinkish-brown circular patch on the dorsum of the foot	[18]
10	15/C/F/PD	3 years	NL: yellowish-brown plaque with ulceration on right pretibial region GA: diffuse brown patch with small papules on left upper leg	[18]
11	67/C/F/DM2	15 years	NL: erythematous annular plaques with atrophic center on bilateral lower extremities GA: erythematous papules and plaques with central clearing on trunk and wrists	[CR]

AA = African American; **C** = Caucasian; **CR** = Current Report; **DM1** = Diabetes Mellitus type 1; **DM2** = Diabetes Mellitus type 2; **F** = female; **M** = male; **MODY** = Maturity Onset Diabetes of the Young; **ND** = no diabetes **NR** = not reported; **PD** = pre-diabetic; **Ref** = References; **SA** = South Asian American.

associated with HIV and paraneoplastic syndromes while NL does not share these associations [20-22].

In 1934, Ketron suggested that NL might be a variant of GA based on histologic findings [25]. In a publication in 1941, Francis Ellis suggested that the lesions of GA and NL could be the same entity [26]. Dr. Ellis mentions the first patient with both GA and NL in a manuscript by Wood and Beerman [19]. In 1968, the topic was readdressed by Fred Feldman, who presented the first case report primarily focusing on GA and NL in the same patient [13]. In this paper, Paul Hirsch mentions the presence of GA and NL in the same patient could possibly yield credence to a unifocal pathogenesis [13].

Treatment of GA and NL can include intralesional triamcinolone, short courses of systemic steroids, and topical steroids [3,4,11]. Other therapies used for GA have included dapsone, imiquimod, topical nitrogen mustard, topical reti-

TABLE 2. Similarities and differences of granuloma annulare and necrobiosis lipoidica [1-11,13-14].

	Granuloma Annulare	Necrobiosis Lipoidica	Both Dermatoses
Clinical Features	• grouped papules • more common on hands and arms • without ulceration	• plaques with violaceous rim and yellowbrown atrophic centers • telangiectasias • more common on lower leg • ulceration can occur • decreased sensation	• annular lesions • rarely involving the face
Epidemiology			• more common in women
Histology	• increased mucin deposition in areas of granulomatous inflammation • can have infiltrative pattern , palisading granuloma pattern, and/or epithelioid nodule (sarcoidal granuloma) pattern	• diffuse inflammation involving dermis and subcutaneous fat • plasma cells • vessel changes including deposition of PASpositive material • endothelial proliferation • telangiectatic vessels • ulceration	• early lesions with leukocytoclasia • necrobiosis with an infiltrate of histiocytes and lymphocytes • epithelioid cells
Disease Associations	• thyroid disease • systemic sarcoidosis • HIV infection • malignancy • paraneoplastic with lymphoma • lipid abnormalities		• diabetes mellitus
Treatment	• isotretinoin • dapsone • antibiotics (minocycline, ofloxacin, rifampin)	• stanozolol • nicofuranose • ticlopidine • TNF alpha inhibitors • tretinoin • thalidomide • mycophenolate mofetil	• topical and intralesional steroids • UV therapy • antimalarials • pentoxifylline • niacinamide
Postulated Pathogenesis	• delayed type hypersensitivity • trauma • insect bite reaction	• immune mediated vascular disease • microangiopathic vessel changes	

noids, and ultraviolet light [1,3]. Our patient's NL lesions were treated with intralesional Kenalog® with improvement; anecdotally, the patient reports her NL had significant improvement after she began a diet and exercise regimen and subsequently lost 15 pounds. Intralesional Kenalog, pentoxifylline, and Plaquenil® have been utilized in the treatment of the patient's GA lesions without benefit.

Conclusion

NL and GA are two disease entities that have many similarities and differences. Rarely, both diseases have been found to occur in the same patient. The two diseases share some common characteristics, which may suggest these dermatoses could occur as a spectrum in some patients. We report the eleventh example of a patient with both GA and NL and describe the characteristics of patients with concomitant GA and NL. Further studies and evaluation needs to be performed to further elucidate the mechanisms and to discover if these disease entities are related.

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