Bilateral skin lesions on the legs

Azmy Abdullatif,[1] MD, Bayoumi Essa,[2] MD

[1]*Professor & Head Department of Dermatology, Al Azhar University, Cairo, Egypt*
[2]*Consultant Dermatologist, Farwaniya Hospital, Kuwait*

A 41-year-old female patient presented with asymptomatic skin lesions on both legs since 4 years. The lesion started as a small skin colored papule on the left leg and spread gradually to involve both legs. Although the lesions were mostly asymptomatic, the patient was complaining from minimal episodes of itching. The patient had a history of diabetes mellitus since 7 years that was treated initially with oral hypoglycemic, and was shifted to insulin therapy 3 years ago. There was no family history of similar condition, and no history of any known systemic illness.

Cutaneous examination revealed bilaterally symmetrical papular lesions on both legs (Fig. 1). The lesions were observed more on the anterior aspects of the legs when compared to the calf area. Some lesions extended into the dorsal aspect of the feet. The lesions were coalescent in some areas to form large patches and plaques. The surface of the lesions was mostly erythematous and scaly. Mild induration was observed in some plaques (Fig. 2). Examination of other body areas showed no similar lesions. Hair, nail and mucous membranes were normal. Routine laboratory investigations showed hyperglycemia and elevated serum bilirubin level.

What is the clinical diagnosis?

1. Psoriasis
2. Sarcoidosis
3. Pigmented Purpuric Dermatosis
4. Necrobiosis Lipoidica
5. Eruptive xanthoma
6. Necrobiotic xanthogranuloma

Elliptical biopsy was performed and histological examination revealed interstitial and palisaded granulomas that involve the dermis and subcutaneous tissue (Fig. 3). The granulomas were arranged in a tier-like (layered) fashion and are admixed with areas of collagen degeneration

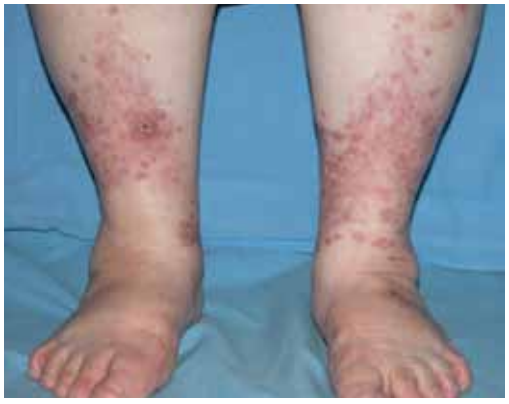

Fig. 1 Bilateral and symmetrical papular lesions on both legs.

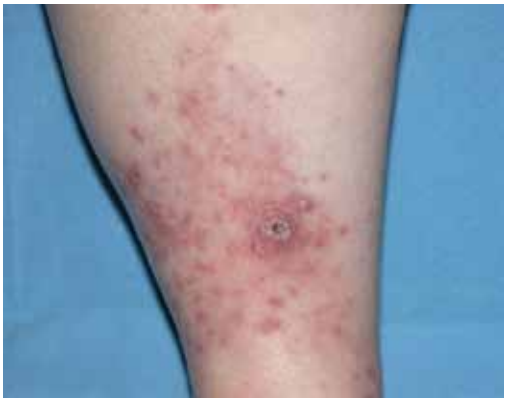

Fig. 2 The lesions were coalescent in some areas to form large patches and plaques. The surface of the lesions was mostly erythematous and scaly.

(Fig. 4). The granulomas were composed of histiocytes, lymphocytes, plasma cells, and occasional eosinophils (Fig. 5). Multinucleated giant cells were abundant with frequent foreign body type (Fig. 6). Alcian blue staining showed no mucin deposition.

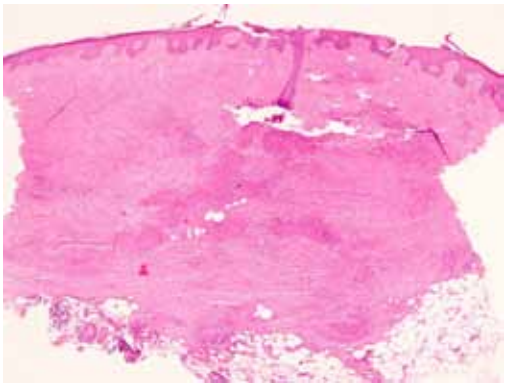

Fig. 3 Interstitial and palisaded granulomas that involved the dermis and subcutaneous tissue.

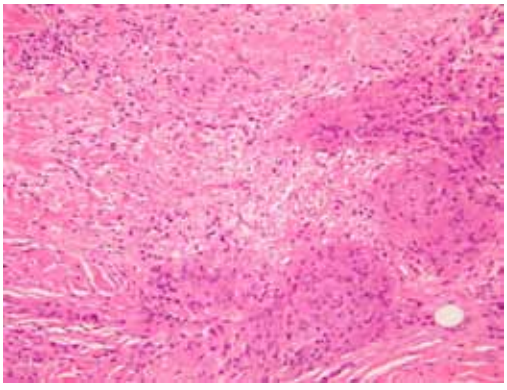

Fig. 4 The granulomas arranged in a tier-like (layered) fashion admixed with areas of collagen degeneration.

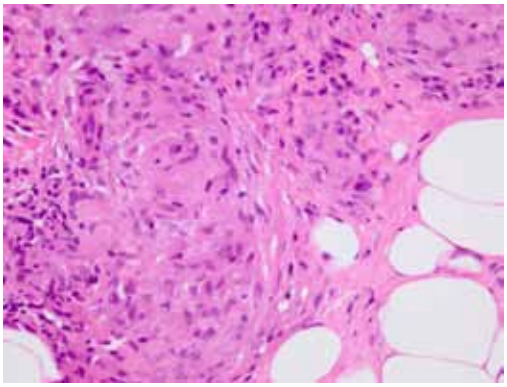

Fig. 5 The granulomas composed of histiocytes, lymphocytes, plasma cells, and occasional eosinophils.

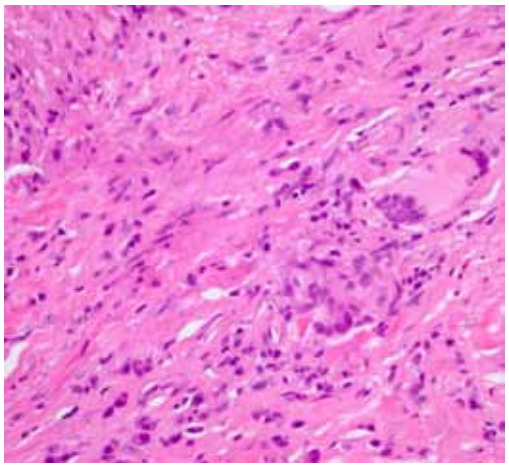

Fig. 6 Multinucleated giant cells abundant with frequent foreign body type.

DIAGNOSIS

Necrobiosis Lipoidica

DISCUSSION

Necrobiosis Lipoidica (NL) is a rare inflammatory granulomatous skin disorder occurring as a result of collagen degeneration, and closely associated with diabetes mellitus. The disease is more common in women than men, and in adults than children. The association between NL and diabetes mellitus (DM) was proposed in numerous studies. It was suggested that more than fifty per cent of NL patients have concurrent diabetes; however diabetic patients also suffering from NL are less than one per cent.[1-3]

The etiology of NL is still obscure. Focal degeneration of collagen is considered to be the initiating event. Due to its strong relationship with diabetes, many studies have focused on the deposition of a glycoprotein material as in diabetic microangiopathy. Other theories implicate an antibody-mediated vasculitis which may initiate the blood vessel changes and subsequent necrobiosis in NL. Perivascular immunoglobulin deposits suggest that NL may be an immune complex vasculitis, except that

the vasculitis is not demonstratable on biopsy specimens.[4,5]

NL is characterized clinically by well-circumscribed erythematous plaques mostly involving the tibial region of the lower extremities. However, involvement of other sites of the body has also been proclaimed. The lesions are commonly subject to ulcerations as a result of trauma, and cannot always be differentiated from those of other inflammatory skin disorders.[6,7]

Three histopathological patterns of NL have been described in literature: the palisading granulomatous pattern, the tuberculoid pattern, and the intermediate pattern. Rarely, transepidermal elimination and lymphoid follicle formation have been seen. Classically, skin biopsy shows sandwich-like horizontal layers of necrobiotic collagen alternating with inflammatory cell infiltrate of lymphocytes, histiocytes, multinucleated giant cells and plasma cells. These changes involved the full thickness of the dermis sparing the subcutis. Reduction in the number of intradermal nerve is an additional feature of NLD. The main findings on histopathology is thickening of the blood vessel walls and endothelial cell swelling found in the middle to deep dermis, the characteristics shared with diabetic microangiopathy.[8-10]

The main differential diagnosis of NL is granuloma annulare (GA), sarcoidosis and necrobiotic xanthogranuloma. GA is found most commonly in children and in adult females <30 years. It usually manifests as groups of 1 to 2 mm papules that range in color from skin colored to violaceous, often in an annular arrangement over distal extremities. Grouped lesions may expand into annular plaques or nodules measuring 1-5 cm in diameter. Histologically, there are not as many plasma cells, and necrobiosis found as seen in NL. Mucin stains such as colloidal iron and alcian blue may be used to highlight the increased connective tissue mucins in granuloma annulare, which is negative in NL (lacks mucin).[11]

Sarcoidosis manifests as maculopapular eruption, with erythema nodosum being the most common lesion. It is usually associated with involvement of other systems like eye, lungs, musculoskeletal systems, lymph nodes, etc. Histologically, sarcoidosis is characterized by naked tubercle with rim of lymphocytes surrounding the epithelioid histiocytes. Plasma cells and necrobiosis of collagen are rarely present in sarcoidosis.[12]

NL undergoes spontaneous remission in less than 20% of cases. Ulceration is the most frequent and hard to treat complication of NL, and is seen in 25-33% of patients. Additionally, squamous cell carcinoma developing in areas of NL has also been reported. Although there are plenty therapeutic options for NL, its treatment is still challenging and sometimes ineffective. First-line treatment includes corticosteroids, either topically or intralesionally, and sometimes systemically. According to some reports, smoking cessation and blood glucose control is helpful. Other therapeutic options are antiplatelet agents, cyclosporine, thalidomide, clofazimine, anti-TNF agents, fumaric acid esters, PUVA, photodynamic therapy, hydroxychloroquine and tacrolimus.[13]

Topical and intralesional steroids can lessen the inflammation of early active lesions and the active borders of enlarging lesions, but these have little beneficial effect on atrophic lesions that are burned out. In fact, with atrophic lesions, steroid use may cause further atrophy. Intralesional

triamcinolone has been reported as effective, and the natural concern regarding the risk of inducing further atrophic change or ulceration may not be warranted according to this study. It was proposed that the topical application of clobetasol propionate under polythene occlusion is an effective treatment method, and a short course of systemic corticosteroid may rapidly resolve the inflammatory element of NL, although the issue of glycemic control with prednisolone in diabetes would require consideration.[14,15]

Recently, immunomodulatory drugs have shown promising results in ulcerating NL. Case studies of cyclosporin used for ulcerating NL reported healing of the ulcers, usually without immediate relapse, although with questionable benefit to the remainder of the lesions. Cyclosporin inhibits interleukin 2 production by T-helper cells, preventing clonal T-cell proliferation, and thereby possibly suppressing the immune response in NL.[16] Mycophenolate mofetil, which has a potent cytostatic effect on lymphocytes, has also been reported to accelerate the healing of ulcerated NL in a nondiabetic patient whose ulceration of 18 months duration healed within 4 weeks of commencing treatment, only to recur on stopping it.[17]

Infliximab, a monoclonal antibody to tumor necrosis factor (TNF)-α, has proved to be a promising therapeutic agent for a variety of inflammatory dermatoses. There is a single-case report of its successful use in recalcitrant ulcerated NL, in a patient with insulin-dependent diabetes, although the recipient developed miliary tuberculosis during treatment. Nonetheless, TNF-α antagonists may prove helpful in NL unresponsive to other treatment modalities. Nonetheless, TNF-α antagonists may prove helpful in NL unresponsive to other treatment modalities.[18]

The surgical management of NL has proponents, although its rationale is still not clear. It has been recommended that excision down to deep fascia or periosteum is undertaken, followed by split skin grafts to cover the defect. However, the tendency of NL to koebnerize on surgical scars means that curative surgery cannot be guaranteed. Moreover, the inevitable resulting disfigurement in a cosmetically sensitive site such as the shins of young women is a major disadvantage. Two single-case studies of the use of the pulsed dye laser to treat the prominent vascular component of NL have been published: one demonstrated a cosmetic improvement in erythema and telangiectasia, and the other reported skin breakdown with higher fluences, with the authors advising caution with respect to laser surgery.[19,20]

REFERENCES

1. Aslan E, Körber A, Grabbe S, Dissemond J. Successful therapy of ulcerated necrobiosis lipoidica non diabeticorum with cyclosporine A. Hautarzt. 2007; 58(8):684-88.
2. Hammami H, Youssef S, Jaber K, Dhaoui MR, Doss N. Perforating necrobiosis lipoidica in a girl with type 1 diabetes mellitus: a new case reported. Dermatol Online J. 2008; 14:11.
3. Szabo RM, Harris GD, Burke WA. Necrobiosis lipoidica in a 9-year-old girl with new-onset type II diabetes mellitus. Pediatr Dermatol. 2001; 18:316-19.
4. O'Toole EA, Kennedy U, Nolan JJ, Young MM, Rogers S, Barnes L. Necrobiosis lipoidica: only a minority of patients have diabetes mellitus. Br J Dermatol. 1999; 140:283-86.
5. Cohen O, Yaniv R, Karasik A, Trau H. Necrobiosis lipoidica and diabetic control revisited. Med Hypotheses. 1996; 46:348-50.
6. Gullo D, Latina A, Tomaselli L, Arpi ML, Squatrito S,

Curatolo S, La Greca S, Vigneri R. Healing of chronic necrobiosis lipoidica lesions in a type 1 diabetic patient after pancreas-kidney transplantation: a case report. J Endocrinol Invest. 2007; 30:259-62.
7. Kota SK, Jammula S, Kota SK, Meher LK, Modi KD. Necrobiosis lipoidica diabeticorum: A case-based review of literature. Indian J Endocrinol Metab. 2012; 16:614-20.
8. Boulton AJ, Cutfield RG, Abouganem D, Angus E, Flynn HW Jr, Skyler JS, Penneys NS. Necrobiosis lipoidica diabeticorum: a clinicopathologic study. J Am Acad Dermatol. 1988; 18:530-37.
9. Abdulla FR, Sheth PB. A case of perforating necrobiosis lipoidica in an African American female. Dermatol Online J. 2008; 14:10.
10. Alegre VA, Winkelmann RK. A new histopathologic feature of necrobiosis lipoidica diabeticorum: lymphoid nodules. J Cutan Pathol. 1988; 15:75-77.
11. Rupley KA, Riahi RR, Hooper DO. Granuloma annulare and necrobiosis lipoidica with sequential occurrence in a patient: report and review of literature. Dermatol Pract Concept. 2015; 5:29-34.
12. Gudmundsen K, Smith O, Dervan P, Powell FC. Necrobiosis lipoidica and sarcoidosis. Clin Exp Dermatol. 1991; 16:287-91.
13. Patsatsi A, Kyriakou A, Sotiriadis D. Necrobiosis lipoidica: early diagnosis and treatment with tacrolimus. Case Rep Dermatol. 2011; 3:89-93.
14. Goette DK. Resolution of necrobiosis lipoidica with exclusive clobetasol propionate treatment. J Am Acad Dermatol. 1990; 22:855-56.
15. Taniguchi Y, Sakamoto T, Shimizu M. A case of necrobiosis lipoidica treated with systemic corticosteroid. J Dermatol. 1993; 20:304-07.
16. Stanway A, Rademaker M, Newman P. Healing of severe ulcerative necrobiosis lipoidica with cyclosporin. Australas J Dermatol. 2004; 45:119-22.
17. Reinhard G, Lohmann F, Uerlich M, Bauer R, Bieber T. Successful treatment of ulcerated necrobiosis lipoidica with mycophenolate mofetil. Acta Derm Venereol. 2000; 80:312-13.
18. Kolde G, Muche JM, Schulze P, Fischer P, Lichey J. Infliximab: A promising new treatment option for ulcerated necrobiosis lipoidica. Dermatology. 2003; 206:180-81.
19. Ghate JV, Williford PM, Sane DC, Hitchcock MG. Necrobiosis lipoidica associated with Kobner's phenomenon in a patient with diabetes. Cutis. 2001; 67:158-60.
20. Moreno-Arias GA, Camps-Fresneda A. Necrobiosis lipoidica diabeticorum treated with the pulsed dye laser. J Cosmet Laser Ther. 2001; 3:143-46.