CASE REPORT

The many faces of necrobiosis lipoidica: a report of three cases with histologic variations

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Abstract

Necrobiosis lipoidica (NL) is a granulomatous disease with unknown etiology and pathogenesis. Clinically, it is characterized by yellow-brown atrophic plaques with inflammatory rims on shins. Histologically, it shows diffused palisade and interstitial granulomatous dermatitis with focal connective tissue degeneration (necrobiosis). We described three non-diabetic NL cases with unusual histologic features. All patients presented erythematous to brownish plaque(s) on the shin(s). In Case 1, in addition to the characteristics of NL, the biopsy showed dense perineural infiltration, which may explain the pathogenesis of the anesthesia of NL lesions. In Case 2, well-formed tuberculoid granulomas were of special interest. In Case 3, there was conspicuous lobular panniculitis. These histologic features present difficulties in the diagnosis and represent the broad spectrum of NL lesions, histologically.

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Introduction

Necrobiosis lipoidica (NL), first coined by Urbach in 1932 as necrobiosis lipoidica diabeticorum, is a granulomatous disease of unknown etiology and pathogenesis. It was named after characteristic histologic findings and was first described in patients with diabetes mellitus (DM). In the largest series to date, Muller and Winkelmann1 found that 111 of 171 patients (65%) with NL had DM at presentation. However, in 1999, a study of 65 patients with NL found only 11% of patients had DM at the time of presentation; an additional 11% were later diagnosed with impaired glucose tolerance or DM. Although lacking full concordance, NL remains an important cutaneous marker of DM.

Clinically the characteristic lesions are inflammatory sclerodermiform plaques on the shins.2 Histopathologically, the hallmark of NL is the linear tiers of palisading necrobiotic granulomas aligned parallel to the skin surface, usually centered in the lower dermis. The superficial dermis and subcutaneous fat, mainly in the septa, may also be affected. The foci of necrobiosis consist of eosinophilic, swollen and degenerated collagen, often appearing hyalinized with surrounding infiltrate of variable numbers of lymphocytes and histiocytes. Plasma cells are almost invariably present and vascular changes are often seen.3 We report three nondiabetic patients with final diagnoses of NL, each having histopathologic features that deviate from the usual pattern. We will elaborate on these interesting and easily misleading findings and review the literature.

Case report

Case 1

A 44-year-old woman presented with partially anesthetic, slowly enlarging skin lesions on the right shin for years. She denied any past medical conditions but complained of numbness of bilateral arms and fingers for several months. A dermatologic examination revealed an erythematous to yellowish plaque with telangiectasia on the right shin. The histopathology of an incisional biopsy showed the characteristics of NL (Figure 1A), namely, the presence of horizontally oriented granulomas with lymphocytes and histiocytes, multinucleated giant cells, prominent plasma cells in the deep dermis, and thickened blood vessel walls. There was necrobiosis but no mucin deposition under Alcian blue stain. The Periodic acid-Schiff (PAS) stain failed to demonstrate any microorganism. Of interest, in deep dermis, there was conspicuous lobular panniculitis. These histologic features present difficulties in the diagnosis and represent the broad spectrum of NL lesions, histologically.

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leprosy, Wade-Fite stain was performed and *Mycobacterium leprae* were not found. Negative result of polymerase chain reaction for mycobacteria provided further evidence that it was not leprosy. A neurologist was consulted about the numbness of fingers and arms, and a study of nerve conduction velocity suggested bilateral carpal tunnel syndrome. The final diagnosis was NL, although there was conspicuous perineural inflammation.

**Case 2**

A 34-year-old woman presented with five asymptomatic gradually enlarging skin lesions on both shins for years. She had a medical history of von Willebrand disease. On physical examination, there were erythematous to brownish shining plaques on both shins (Figure 2). The specimen from an incisional biopsy showed granulomatous inflammation involving the full thickness of the dermis and part of the subcutis. The inflammatory infiltrates were composed of epithelioid histiocytes, plasma cells, Langhans’ giant cells, and foreign body type giant cells, focally associated with lymphocytic aggregates. In the dermis, focal collagen degeneration was noted (Figure 3A). The epidermis displayed no significant change. Both PAS stain and acid-fast stain demonstrated no microorganism. The histiocytes expressed no S-100 protein. Of special interest were several well-formed tuberculoid granulomas in the specimen without caseous necrosis, a few “naked granulomas” (Figure 3B), and occasional asteroid bodies (ABs) (Figure 3C) in epithelioid histiocytes. The final diagnosis was NL with prominent tuberculoid granulomas.

**Case 3**

This 53-year-old woman complained of asymptomatic skin rashes bilaterally on the shins for 2 months. A dermatologic examination revealed one irregular well-demarcated, brownish, shiny, indurated plaque with a violaceous periphery on the left shin (Figure 4A), and several round patches with mildly atrophic centers and brownish peripheries on the right lower leg. An incisional biopsy was performed at the periphery of the lesion on the left shin. Microscopically, it showed granulomatous inflammation composed of mononuclear and multinucleated macrophages affecting the deep dermis and subcutaneous fat (Figure 4B). In the deep dermis and septae of panniculus, degenerative collagen fibers with swelling and hyalinization were present. Mild blood vessel proliferation and sclerosis were found in the dermis. No vasculitis was observed. There was no obvious mucin deposition in the dermis. The PAS and acid-fast stains failed to demonstrate any microorganisms. Based on the above features, NL with granulomatous lobular panniculitis was diagnosed.

**Discussion**

The three cases are linked by their common histopathological findings of palisading necrobiotic granuloma and lymphoplasmocytic infiltrate, both characteristic of NL. However, the unusual features that are displayed by the three cases expand the spectrum of NL. These include the presence of perineural inflammation in Case 1, prominent tuberculoid granulomas in Cases 2 and 3, and prominent lobular panniculitis in Case 3.

In Case 1, NL was strongly suspected at the first sight of the section. The absence of mucin deposition and the presence of a large amount of plasma cells made granuloma annulare (GA) an important differential diagnosis of NL, less likely. Not until the perineural inflammatory cell infiltrates were noted histologically was the differential diagnosis of leprosy considered. Looking
might be considered. Histopathologically, the dense in erythematous plaque, a diagnosis of tuberculoid leprosy (TT) back on her clinical presentation of a solitary anesthetic annular lymphocytes, histiocytes, and Langhans' type giant cells. Necrobiosis is present in the lower area of this picture (hematoxylin and eosin (H&E), 40×). (B) Well-formed tuberculoid granulomas and numerous plasma cells (H&E, 100×). (C) Asteroid body (arrow) (H&E, 400×).

Figure 3 Case 2. (A) The histopathology shows tuberculoid granuloma consisting of lymphocytes, histiocytes, and Langhans' type giant cells. Necrobiosis is present in the lower area of this picture (hematoxylin and eosin (H&E), 40×). (B) Well-formed tuberculoid granulomas and numerous plasma cells (H&E, 100×). (C) Asteroid body (arrow) (H&E, 400×).

were a large number of plasma cells surrounding the nerve, which are rarely seen in leprosy but almost invariably present in NL. Furthermore, there was no nerve destruction or granulomatous neuritis typical of TT and BT. Taken together, along with the negative Wade-Fite stain and polymerase chain reaction results, we excluded the diagnosis of leprosy. The carpel tunnel syndrome in this case was thought to be a coincidence.

Partial or complete anesthesia of the NL plaques was first reported by Mann and Harman and then confirmed by Boulton et al. Most of the subjects in those two studies had a decrease or absence of at least one cutaneous sensory modality. Boulton et al declared that the staining intensity of cutaneous nerves for S100 protein diminished within the areas affected by inflammatory infiltrate in NL. A further study in 2008 documented the absence of nerve fibers as demonstrated by antineurofilament and peripherin in the central areas of the necrotic foci, which might explain the anesthesia. Despite such studies suggesting that local destruction of cutaneous nerves was caused by the inflammatory process, they did not present any evidence of this mechanism. Case 1 was the first reported case of NL revealing lymphoplasmocytic infiltrates surrounding the cutaneous nerve, and we believe it offered direct evidence that the sensory nerve defect in NL was probably because of the perineural inflammatory process. On the other hand, anesthesia that is associated with NL could relate to microvascular injury, which can lead to axonal degeneration, resulting in significant small sensory fiber abnormalities.

In Case 2, NL, GA, infectious disease, and Rosai-Dorfman disease were considered histopathologically. NL and GA are both characteristic of necrobiosis and palisading granuloma; however, the large amount of plasma cells in this case favored a diagnosis of NL. Rosai-Dorfman disease and fungal and mycobacterial infectious granuloma could be ruled out by S-100 protein and PAS and acid-fast stain, respectively. It is worth noting that other than palisading granulomas, there were several well-formed tuberculoid granulomas. According to Muller and Winkelmann, NL lesions can be classified histopathologically into two groups (1) a palisading granulomatous type; (2) a tuberculoid or sarcoideal type, which is characterized by the presence of many epithelioid cells and giant cells frequently grouped in pseudotubercles. The latter type was named necrobiosis lipoidica granulomatous (NLG) and was believed to be identical to Miescher's granuloma or granulomatosis disciformis chronica et progressiva (GDCP) described early in 1948. Using the classifications above, Case 2 could belong to necrobiosis lipoidica granulomatous or GDCP.

In Case 3, the foci of epithelioid cells frequently were grouped in pseudotubercles similar to the microscopic pattern of Case 2. Of interest, these pseudotubercles involved extensive fat lobules, in addition to classically deep dermis and fat septae. Other lobular granulomatous panniculitis, such as tuberculosis, erythema induratum, or subcutaneous sarcoidosis, may be considered. The negative result of acid-fast stain and the absence of vasculitis ruled out tuberculosis and erythema induratum, respectively. The most characteristic feature supporting a diagnosis of NL in this case rather than subcutaneous sarcoidosis was the characteristic changes in the dermis, with granulomatous inflammation and the hyalinized and necrobiotic collagen fibers. This case is unique in its extensive lobular panniculitis, which has never been mentioned in association with NL.

It is worth mentioning that ABs were seen in Cases 2 and 3. A review of literature revealed only three cases of NL associated with ABs. ABs are a nonspecific product of giant cell formation and observed nonspecifically in many granulomatous reactions. There are many possible constituents of ABs, such as proteinaceous material, microfilaments and microtubules, and collagen. Laminar and tubular osmiophilic lipid structures, lipoprotein
related with the local destruction of lipids, vimentin filaments mediated by the extensive lipid component, and complex lipids (mostly phospholipids) secondary to the excess cellular and lysosomal membranes present after macrophage activation and fusion have also been reported as principle components of ABs. Accordingly, ABs can be found in NL, a disease in which the deposition of lipids is frequent, and especially in the tuberculoid type, because of the formation of numerous multinucleated giant cells.

In summary, we present three cases of NL with shared histopathologic features that mimic leprosy and/or tuberculosis. Unusual presentations like these make dermatologists and dermatopathologists more aware of the broad pathologic spectrum of the disease. The first case revealed typical NL, except for perineural inflammatory cell infiltrates, an exceedingly rare finding in NL lesions. This makes leprosy an important differential diagnosis and may explain, at least in part, the pathogenesis of the anesthesia in NL lesions. The other two patients could be categorized as having tuberculoid/sarcoideal type NL, or using the old fashioned term, as GDCP. These are the fourth and fifth reported cases of NL with ABs, which might be more likely to be present in the tuberculoid/sarcoideal type than in the palisading type of NL.

References

Figure 4 Case 3. (A) Irregular, well-demarcated, brownish, shiny, indurated plaque with violaceous periphery on the left shin. (B) Granulomatous inflammation affecting the deep dermis and subcutaneous fat (hematoxylin and eosin [H&E], 40x). (C) Degenerative collagen fibers with swelling and hyalinization in deep dermis (H&E, 100x). (D) Lobular granulomatous panniculitis with several types of giant cells, including Langhans’ type, foreign body type, and osteoclast-like giant cells. Lipomembranous change is seen (H&E, 100x).