Granuloma Multiforme in India

Leiker[1] in 1964 coined the term granuloma multiforma, "a disease resembling leprosy," to describe an entity with "a granulomatous structure and variation in clinical aspect." He described the profile of 148 such patients found in a survey in northern Nigeria. Soon after, Browne[2] reported cases from eastern Nigeria and Meyers, *et al.*,[3] from the Congo. Most patients were found in leprosy settlements, where they were mistakenly undergoing treatment for leprosy.

The etiology[1, 2] of this disease is yet to be elucidated. Airborne agents from roofing and headloads, as well as parasites such as microfilariae, have been seriously considered.

We report on two patients with granuloma multiforme who presented at a small leprosy center in South India. The clinicohistological picture seen was identical to that described by Leiker.

Case 1. A 75-year-old female presented with skin lesions associated with a mild burning sensation of 1-year duration.

Examination revealed 8 to 10 lesions distributed over the arms, back and forearms. They ranged in size from ½ cm to 10 cm. All of her lesions were rimmed by an erythematous or flesh-colored papular border. The larger lesions showed mild atrophy and hypopigmentation of the central areas; whereas this feature was not marked in the smaller lesions. There was no sensory loss or peripheral nerve thickening. Over the next 4 months, she was observed to develop new lesions on the flanks, forearms and dorsum of the hand. The patient was then lost to follow up.

Further investigation gave a negative result for skin smear for acid-fast bacilli (AFB). Her ESR was 40 mm in the first hour, and she had a two-hour postprandial blood sugar of 100 mg%.

A skin biopsy from the edge of a large lesion showed dense perivascular and peri-

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[1] Leiker, D. L., Kok, S. M. and Spaas, J. A. J. Granuloma multiforme, a new skin disease resembling leprosy. Int. J. Lepr. **32** (1964) 368–376.

[2] Browne, S. G. Granuloma multiforme in eastern Nigeria. Int. J. Lepr. **34** (1966) 27–29.

[3] Meyers, W. M., Connor, D. H. and Shannon, R. Histological characteristics of granuloma multiforme. Int. J. Lepr. **38** (1970) 241–249.

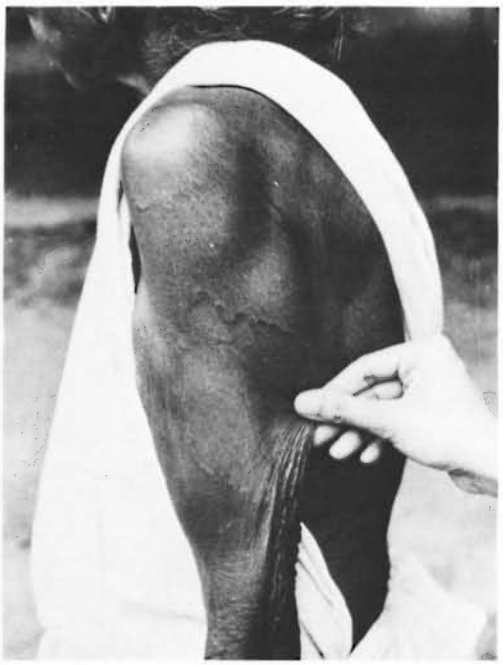

FIG. 1. Large, well-defined lesions with raised borders on the arm and shoulder; central area shows hypopigmentation.

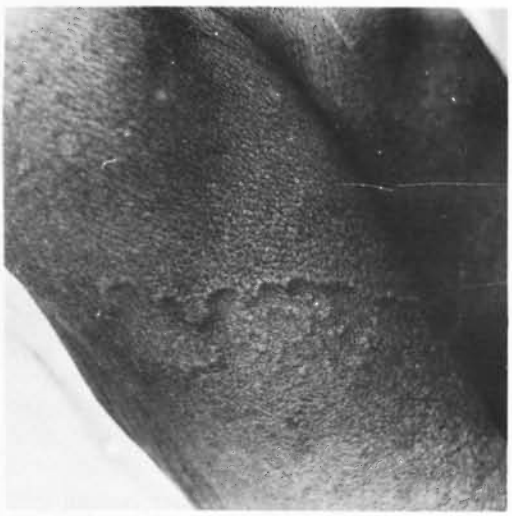

FIG. 2. Close up of raised border of Fig. 1 lesion showing closely set papules.

adnexal aggregates of lymphocytes. There were foci of collagen degeneration surrounded with an inflammatory reaction composed of many histiocytes and multinucleated giant cells. A dense perineural collection of lymphocytes was seen in the mid-dermis and in one prominent nerve in the deeper dermis, with one or two lymphocytes within the nerve. No AFB were present.

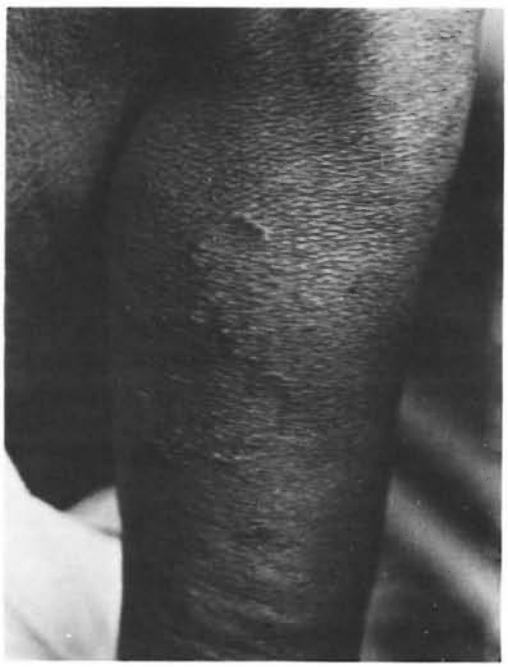

FIG. 3. Circinate lesions on back of the arm.

Case 2. This 60-year-old female was seen 3 months later. She presented with lesions of 2 years' duration which were itchy initially and extended slowly. She gave no history of contact with leprosy. An examination showed about eight plaques situated mainly on the trunk and upper limbs. The lesions were large, from 5 cm to 15 cm in diameter, irregular in shape, and rimmed by a papular border. The bigger lesions showed central clearing; the others were slightly raised. Again, there was no sensory loss or peripheral nerve thickening.

During subsequent visits, this patient was seen to develop new lesions. A single new lesion on the flank was carefully observed. It began as a papule, and then extended into a plaque with a finely wrinkled surface. A month later it showed central clearing. A few weeks later, the lesions were flat except for the papular margin; the central area then showed mild hypopigmentation. A smear for AFB from the patches was negative. Her ESR was 30 mm/hr and her two-hour postprandial blood sugar was 100 mg%.

Histopathology of the skin from the edge of a plaque showed localized areas of degeneration of collagen in the superficial dermis, some fairly well defined, others relatively ill defined. These areas were associated with an infiltrate of lymphocytes and histiocytes, some of which were epithelioid. One discrete epithelioid granuloma was present, and several multinucleate macrophages were seen. There was focal necrosis of the dermis with considerable disarray of collagen in these areas. A fairly dense perivascular infiltrate was seen, but no vessel-wall thickening. One of the two dermal nerves seen contained a few lymphocytes. AFB and detectable mucin were absent.

Discussion. The clinical features and histology of the lesions described in these two patients are classical for granuloma multiforme. The well-defined nature of the lesions with raised borders and central hypopigmentation closely simulates borderline tuberculoid leprosy. The itching and burning sensation associated with the onset of the lesions mimics the paresthesia sometimes associated with leprosy lesions. Differentiation is based on the absence of objective sensory loss, normal size of peripheral nerves, negative skin smears, and a histological picture of necrobiosis.

Granuloma annulare ties in with leprosy in the differential diagnosis of granuloma multiforme. Unlike granuloma annulare which affects a younger age group, granuloma multiforme is more commonly seen after 40 years of age and is thought to have a female predilection.[2] Again, the large lesions distributed on the back and arms in granuloma multiforme are in contrast to the smaller rings of granuloma annulare seen mainly over the distal parts of the limbs.

Both entities are classified as necrobiotic disorders. Granuloma multiforme differs in the dense perivascular infiltrate seen, the absence of mucin, the absence of palisading of cells and, particularly, the prominent multinucleate giant cells in the infiltrate. Of special interest are the intraneural lymphocytes seen in both of these cases. This feature has not been reported earlier.

Necrobiosis lipoidica shares many histological features with granuloma multiforme, but does not cause confusion on clinical grounds. The distinguishing features are the presence of fibrosis intermingled with the necrosis, vessel-wall changes, and fat deposition. The clinical differentiation is by the yellowish color of the plaques, telangiectasia, and its predilection for the lower limbs.

Tinea corporis is excluded by the absence of scaling and a negative scraping for fungus.

In summary, these two case reports from South India are of patients who presented with granuloma multiforme, an entity thought to be confined to Africa and Indonesia.[4] Interest lies in its possible misdiagnosis as leprosy.

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[4] Leiker, D. L. Differential diagnosis. In: *Leprosy.* Hastings, R. C., ed. London: Churchill Livingstone, 1985, pp. 185–186.