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Ulcerating Lepromatous Leprosy in a Patient with Dapsone-resistant *Mycobacterium leprae**

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While under treatment with dapsone for lepromatous leprosy, a 50-year-old male Greek Cypriot presented with multiple widespread lesions of a bizarre type, many of them freely ulcerating.

Clinically and histologically, peripheral nerves were little affected, but biopsy samples of skin and ulcers contained enormous numbers of leprosy bacilli. Mouse footpad inoculation of the bacilli from skin homogenates showed resistance to all three levels of dapsone tested, namely 0.01, 0.001 and 0.0001% in the diet of mice.

From two of the larger ulcers bacilliferous discharges were collected in occlusive dressings over a 24-h period. Attention is drawn to the very large number of bacilli counted in this discharge. Excluding the nose, the shedding of dapsone-resistant bacilli into the environment from body ulcers in this case could have been in excess of 20 millions daily.

Case Report

Mr C. Z., a Greek Cypriot aged 50, gave a history of leprosy treated in Cyprus for 3 years before his first registration as suffering from lepromatous leprosy in London in 1965. At that time he presented with scattered deep ulcers on the legs and trunk, varying in size from one to several centimetres in diameter, together with a number of infiltrated plaques and nodules. He responded to dapsone, 100 mg twice weekly, and did well until April, 1970, when it was thought that the plaques and nodules had increased. A single skin biopsy at that time failed to reveal any acid-fast bacilli, but was reported as consistent histologically with lepromatous leprosy; routine slit-skin smears revealed only small numbers of degenerate bacilli. The patient continued on the same dose of dapsone, but became irregular during 1971, missing a total of about 5 months' treatment in that year. In November, he presented in Oxford with a remarkable crop of intra- and sub-cutaneous nodules on the arms, legs and trunk (but not on the face or ears), varying from 0.5 to 2 cm in diameter. One or two isolated lesions on the

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trunk were strongly suggestive of histoid leprosy (Wade, 1963; Rodriquez, 1969). Several lesions on the arms and legs (but not those on the trunk) were ulcerating freely (Figs 1 and 2); some had a raised, rolled edge, and others had a surrounding zone of dilated skin vessels. Lesions were neither painful nor tender. The skin between the lesions showed areas of atrophy and sub- and intra-cutaneous induration, suggesting previous inflammation. Lymph nodes in drainage areas were, surprisingly, either normal in size, or impalpable. Peripheral nerves were generally unaffected, only the terminal radials and superficial peroneals showing any definite enlargement; this was bilaterally symmetrical. There was no nerve tenderness in any site, and the patient had no evidence of anaesthetic damage to hands, feet or eyes, despite the fact that he was working as a machine operator in a screw factory. Response to pin-prick was normal throughout, but to cotton wool it was marginally defective in patchy areas on both hands and feet. He had a controlled atrial fibrillation, impalpable apex beat, normal heart sounds and blood pressure, slight pitting oedema of both ankles, and hepatomegaly (3 finger-breadths below the right costal margin). The thyroid gland was not enlarged, and there was neither tremor nor exophthalmos. Other systems gave results within normal limits, and the patient's general appearance and state of nutrition were excellent. His past history was without significant illness, but in October, 1970, he had been admitted to hospital in London with cardiac failure and atrial fibrillation, thought to be due to thyrotoxicosis.

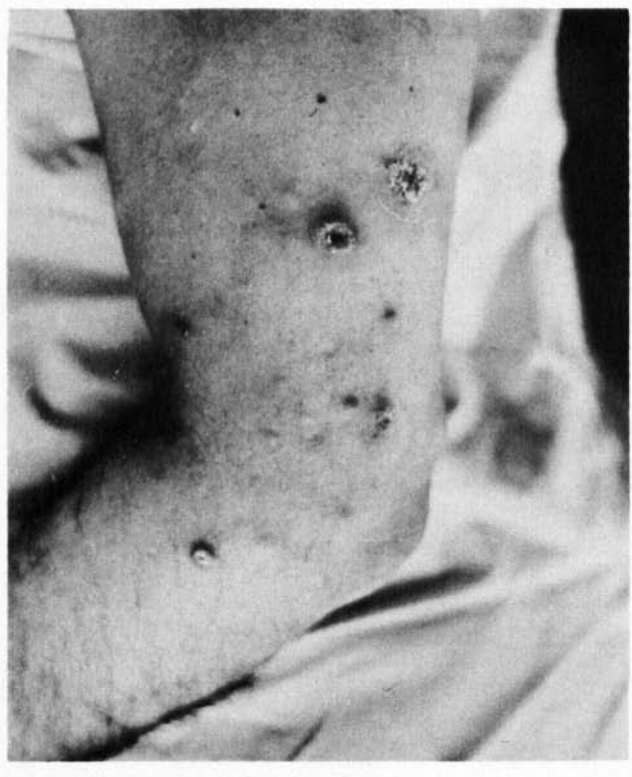

Fig. 1. Left arm.

Investigations

Skin smears from 6 different ulcerating areas showed enormous numbers of acid-fast bacilli; the bacillary index (BI) was 6+ and the morphological index (MI) 28%. Six slit-skin smears taken from between these ulcers, and from skin that appeared to be as normal as possible, gave a BI of only 2, with an MI of 3.

Biopsies were taken from (1) skin nodules, to include neighbouring and apparently normal skin, (2) skin ulcers, to include the edge, and (3) the left radial nerve at the wrist.

The histopathology was as follows.

1. SKIN NODULES

These showed enormous concentrations of bacilli, often to the exclusion of almost everything else in the field, with a high percentage of solid-staining forms. The infiltrate was of histiocytes and fibroblasts; there was an increase of small vessels, some with endothelial swelling. Lymphocytes were not numerous, but plasma cells were conspicuous in some fields. Nerve filaments were not identified in these sections; they may have been obscured by infiltrate.

2. SKIN ULCERS

Here the bacillary concentration and the infiltrate were similar, but merged into an open and partially necrotic zone, where polymorphonuclear leucocytes

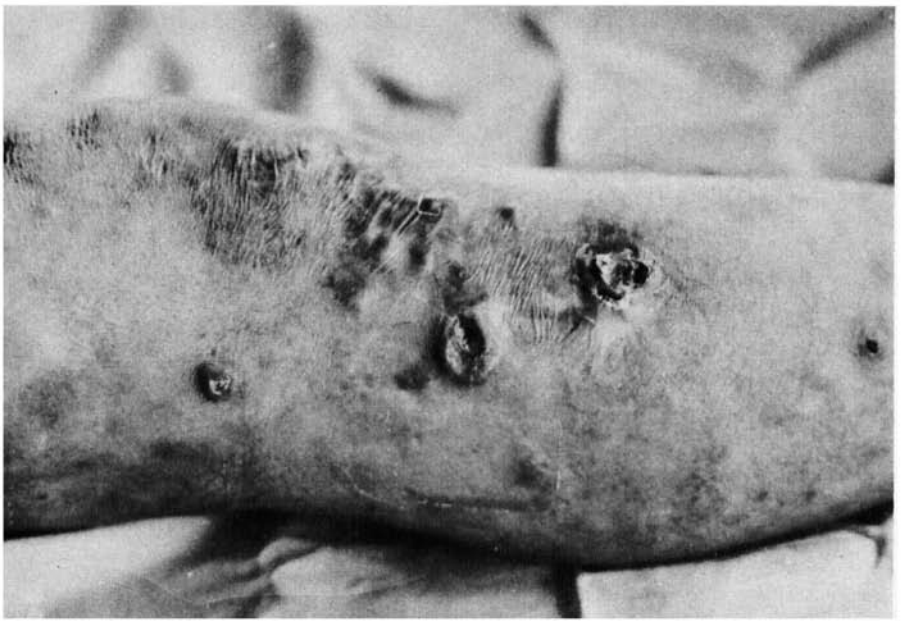

Fig. 2. Knee region.

Ulcerating lesions, together with intra- and sub-cutaneous nodules on presentation in November, 1971. The patient had 7 similar open ulcers, and the excretion from them could have been in excess of 20 million dapsone-resistant bacilli per 24 h.

were common, and bacilli (solid and non-solid) could be seen "flowing out" to the surface.

3. RADIAL NERVE

At the wrist: this showed a quiet, old-looking, lepromatous histopathology with occasional non-solid bacilli lying in foamy macrophages and a scanty infiltrate of lymphocytes and plasma cells. There was minimal endoneurial collagenization. Histologically the picture resembled that seen between nodules or ulcers in the skin.

BACILLARY COUNTS

Homogenization of skin gave a total yield of 5.5×10^8 organisms per g of tissue; the MI was 9. Using the thin plastic covers from proprietary adhesive dressings, collections were made of the discharge from two skin ulcers over a period of 24 h. These together yielded 7.5×10^6 bacilli, with an MI of 20. Nose-blow material (mainly mucus), collected over 24 h, yielded 4.1×10^5 bacilli; MI 18.

DAPSONE SENSITIVITY

Bacilli from the skin, inoculated into mouse footpads, showed complete resistance to the three levels of dapsone used in the test, namely 0.01, 0.001 and 0.0001% in the diet of the mice; the highest level is equivalent to a dose of 100 mg of dapsone daily for man.

OTHER INVESTIGATIONS

These included: haemoglobin, 15.8 g %; leucocytes, 6900; erythrocyte sedimentation rate (ESR) 31; no LE cells were found; immunoglobulins IgG 2170, IgA 725, IgM 250 mg per 100 ml; the Wassermann reaction and Kahn and Reiter's PCFT were all negative as was also the latex screening test (RA); the urine protein level was 78 mg per 100 ml, in a volume of 630 ml; electrolyte, bilirubin, and alkaline phosphatase values were all normal. A chest radiograph with barium swallow showed cardiac enlargement and a prominent left atrium and appendage, the appearances suggesting mitral-valve disease. No lung lesion was seen; the ECG showed atrial fibrillation, but no other change. At the time of the patient's admission to hospital in October, 1970, with heart failure, his ECG showed no evidence of infarction; the P.B.I. was then found to be 8.1, with T3 (Sephadex) 7.2, and T4 8.2.

Progress

The patient's clinical deterioration while being treated with dapsone, 10 years after the initial diagnosis, together with the highly positive skin smears and a histopathology of straightforward ulcerating lepromatous leprosy, suggested there was resistance to dapsone, and this drug was therefore replaced by rifampicin, 600 mg daily. All ulcers healed completely in a matter of days, and many of the intra- and sub-cutaneous nodules became smaller. He was treated throughout as an out-patient; checks of the urine usually, but not invariably, showed the reddish colouring suggestive of regular rifampicin intake. In July, 1972, biopsies from skin and scrotum showed marked histological improvement, and homogenization of the latter yielded 4.1×10^6 bacilli per g of tissue, MI 3 (1/33). At the time of

writing (December, 1972) the patient is extremely well, possibly better than he has ever been since first diagnosis, and there are no clinical signs of lepromatous activity. At no time has he shown any suggestion of *erythema nodosum leprosum* (ENL) or other manifestation of Type-2 reaction.

Discussion

The patient presented himself in November, 1971, for routine checking; he was not seeking advice, and had no general complaints. At this stage, a number of experienced observers were reluctant to admit that his lesions were all ascribable to leprosy, resistant or otherwise, and the possibility of syphilis, tuberculosis, exotic tropical disease, or malignancy was discussed.

An ulcerating form of *erythema nodosum leprosum* was also considered, but skin and ulcer smears, together with the histopathology, soon revealed that this was not the explanation, and that the picture was simply one of ulcerating lepromatous leprosy. In the material obtained by biopsy no histoid features were found, but this may well have been due to the selection of the site for biopsy. The clinical and histopathological "escape", or sparing, of nerves is difficult to understand; in both respects, they seem to have been minimally affected, in contrast to the gross involvement of skin, sometimes only a few millimetres distant. Lymph nodes, even in nearby drainage areas, were also unaffected clinically. In view of his previous experience of skin ulceration in 1965, together with a possible relapse in 1970, and his admission to hospital later that year with cardiac failure, consideration was given to the possibility that thyrotoxicosis might have had a recurring, adverse effect on the lepromatous leprosy. The laboratory findings support this diagnosis; and certainly no other cause has been found for his atrial fibrillation. However, there are no references to this conjunction in the literature, although the converse has attracted more attention, with studies such as those on thyroid and anti-thyroid substances in murine leprosy (Jai-Kyoung Koh *et al.*, 1969), and methimazole in lepromatous leprosy (Levy *et al.*, 1967; Browne and Hogerzeil, 1962; Rojas, 1963). It may be worth recalling that an early publication on thalidomide (Murdoch and Campbell, 1958), now known to be dramatically successful in certain lepromatous reactions, described this drug as having significant anti-thyroid activity.

Of perhaps major interest in this case were the counts of bacilli excreted from skin ulcers over a period of 24 h. The collection of 7.5×10^6 bacilli from two ulcers in 24 h implies that from the 7 open lesions, over 20 million dapsone-resistant organisms per day might well have emerged. This exit route for bacilli into the environment in lepromatous leprosy is often underestimated or overlooked, nasal discharges in lepromatous leprosy usually being of much greater importance. In this case, a 24 h collection of nose-blow material yielded only 4.1×10^5 bacilli—a rather low figure in comparison with the yields obtained from several other patients examined in this unit during the past year, where figures of the order of 3.4×10^8 bacilli per 24 h have been recorded.

Acknowledgements

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