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Histoid Leprosy. An Ultrastructural Observation[1]

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Ever since the first description of histoid leprosy by Wade ([10]), this type of lesion has aroused widespread interest on account of the peculiarity of the spindle-shaped host cell and of the pathogenic mechanism that gives rise to it. There is nothing to suggest that this type of disease is an integral part of the ordinary spectrum of leprosy. Wade refrained from speculation about its causation. Rodriguez ([9]) and Desikan and Iyer ([1]) postulated that it was due to a mutant form of leprosy bacillus associated with sulfone resistance. Pettit, *et al.* ([5]) and Ridley ([6,7]) thought the lesion was essentially a more active form of leproma, without completely explaining it, and Job, *et al.* ([3]) supported this view.

The present study is concerned mainly with the nature of the histoid cell, which Wade regarded as essentially histiocytic. There has been very little dissent from this view, but in the only ultrastructural study so far reported, Job, *et al.* ([3]) found evidence that the cell, though histiocytic, had the characteristics of both macrophage and fibroblast. We report here the electron microscopic findings in a further case.

MATERIALS AND METHODS

The patient was a 23 year old Chinese male with active lepromatous leprosy whose disease was classified clinically and histologically as subpolar lepromatous (LLs). He had received no anti-leprosy treatment. Nodules appeared first on the forearms, and over a period of 3 years more nodules developed on the arms, trunk, and back. The biopsy was taken from a young, active nodule.

The biopsy was cut into two, half being placed in FMA fixative for routine examination by hematoxylin and eosin stain and the Fite stain for acid-fast bacilli, as modified by the Armed Forces Institute of Pathology, U.S.A., ([7]). Other stains included P.A.S. and Mallory's trichrome stain for collagen and also a reticulin stain after Gomori.

The other half was placed in ice cold 3% glutaraldehyde in cacodylate buffer, pH 7.4, and quickly cut into small pieces measuring 1 mm^3. Fixation was carried out for 24 hr after which the specimen was postfixed in osmium tetroxide and embedded in an araldite epon mixture. Semi-thin sections were cut from several blocks and stained in methylene blue-azur-basic fuchsin ([2]). Procedure:

1. Stain in methylene blue-azur at 65°C, 5–15 min.
2. Wash and dry.
3. Stain in basic fuchsin B, 30 sec.
4. Rinse and dry.
5. Mount.

The specimen was examined in an AEI 801 microscope.

RESULTS

Light microscopy. The lesion consisted of a large granulomatous nodule, which extended down into the deep dermis. It was not encapsulated although cells at the upper peripheral margin showed an orientation so as to form a pseudocapsule. These cells appeared similar to those forming the main lesion. Bacilli were seen scattered throughout the lesion, being more numerous in some places than in others. The bacilli were solid staining. No globi were seen. Cells forming the pseudocapsule also contained many solid organisms. No satellite lesions were seen. In the center of the nodule, one area of polymorphonuclear leukocytic infiltration was seen, and here all the medium sized blood vessels showed fibrinous changes with extravasation of blood similar to the changes seen in the vasculitis of erythema nodosum leprosum (ENL). Bacilli in this area were fewer than elsewhere. Lymphocytes were sparse. The host cells had the appearance of very young macro-

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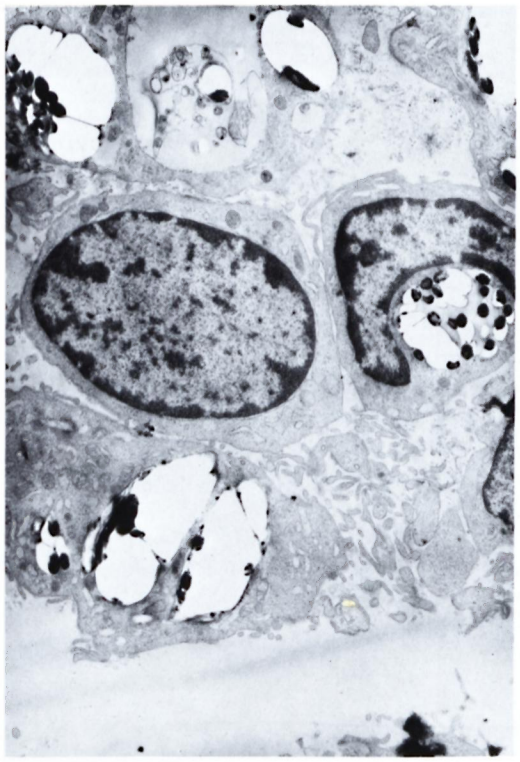

FIG. 1. First variant of macrophage which has characteristics of monocytes. There is poorly developed endoplasmic reticulum, a large nucleus with densely granular cytoplasm. The nucleus to cytoplasm ratio is high in these cells. (×8000)

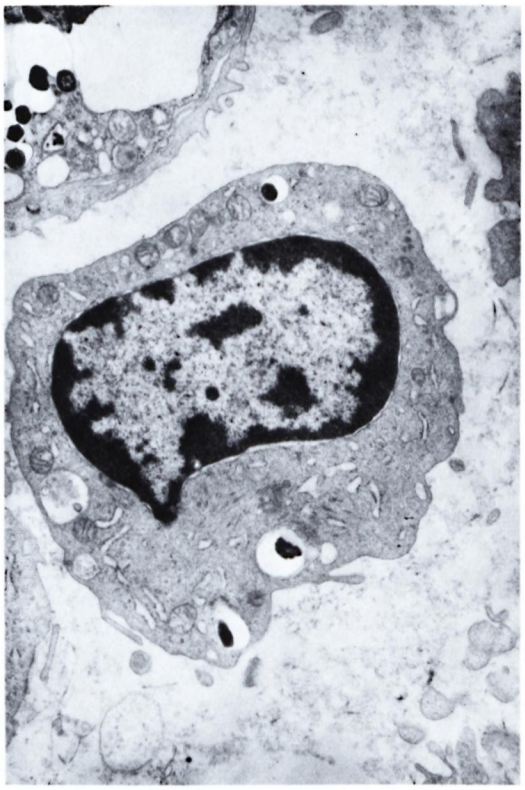

FIG. 2. Second variant of macrophage. There is more abundant cytoplasm than in the first variant and usually a well-developed Golgi apparatus (not seen here). All have single solid bacteria and endocytotic vacuoles in them. (×8000)

phages. No epithelioid cell foci were seen on serial sectioning. No P.A.S. positive material was seen. The reticulin pattern was not increased, and with Mallory's stain the band of cells forming the pseudocapsule alone showed some aniline blue fibrils. These fibrils were not seen in the main granulomatous area.

Electron microscopy. Semi-thin sections were chosen to represent areas passing from the epidermal pseudocapsule through the main granulomatous area to the deep polymorphonuclear leukocytic exudate.

The main cell in the granuloma was a macrophage of which 3 variants of the same cell type were seen. One variant of macrophage was a rounded cell with a very large oval nucleus and sparse cytoplasm containing few mitochondria and a little rough endoplasmic reticulum (RER). The nucleus was densely granular with condensed chromatin, especially on the rim. The cell membrane was distinct with some villous protrusions but no filamentous membraneous projections. The cell resembled a monocyte (Fig. 1). Few cells of this type had ingested bacteria. Another variant of this cell was larger and had more cytoplasm containing RER and mitochondria. This type of cell usually contained bacilli as single solid organisms (Fig. 2). The third variant was a more mature cell of the same size in which the nucleus was uniformly granular. No chromatin condensations were seen. The cytoplasm was filled with bacteria all of which appeared to be solid with an electron transparent zone around them (Fig. 3). Some membrane bound vesicles containing degraded products and granular material were present. RER was inconspicuous. Mitochondria were seen. Golgi apparatus was present. The membrane of this type of cell often appeared

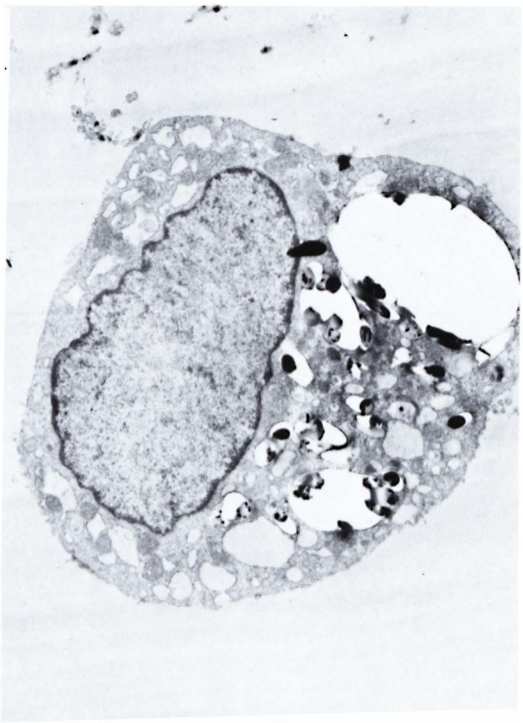

FIG. 3. Third variant of macrophage. All these cells are highly phagocytic with solid bacilli and endocytic vacuoles. The nucleus is pale and granular. The cell margin is indistinct, which may represent the first appearance of cell death. (×8000)

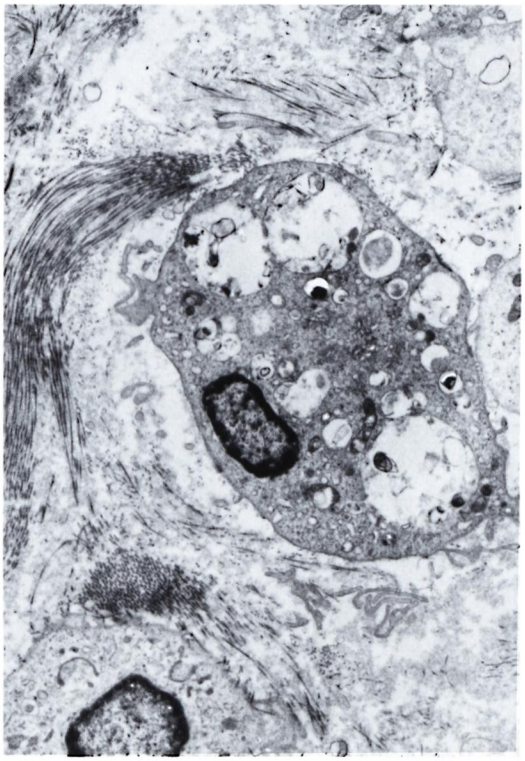

FIG. 4. Collagen fibrils and granular edematous material is found in the interspace between the cells. Endocytic vacuoles are filled with debris. (×8000)

indistinctly. This appeared to be the first sign of cell death, which was readily identified in later stages. Cell debris was ingested by other macrophages. No mitosis was seen. The interspaces between macrophages were occupied by fine collagenous fibers or a finely granular substance, probably edema (Fig. 4).

Plasmacytoid cells were seen in small numbers, scattered among the macrophages. They were distinctive by their abundant cytoplasm and eccentric nuclei (Fig. 5). The nucleus was typically stellate with dense chromatin and pale spaces in between. The cytoplasm was occupied by much RER some of which was dilated to form lakes. Mitochondria and lysosomal bodies were present. No bacteria were seen in any of these cells.

A considerable area surrounding the granuloma formed what appeared to be a pseudocapsule (Fig. 6). It was several layers of cells deep. All the cells were typically spindle shaped as has been described for this form of lepromatous leprosy. However, the cells seemed to represent macrophages similar except in shape to those already described. Many cells, notably those with pale staining nuclei, probably the more mature cells, contained solid bacilli. All these cells were oriented in the same direction and were closely compacted by extending pseudopodia. A few fibroblasts were seen.

In the area of polymorphonuclear leukocytic exudate, there was much phagocytosis of extravasated red blood cells around blood vessels. There was also death and phagocytosis by polymorphonuclear leukocytes and macrophages, of macrophages in this area.

DISCUSSION

Our findings confirm the conclusion of Wade [10] that the cell type in the histoid nodule is of the mononuclear phagocyte series. Three distinct zones were noted as the

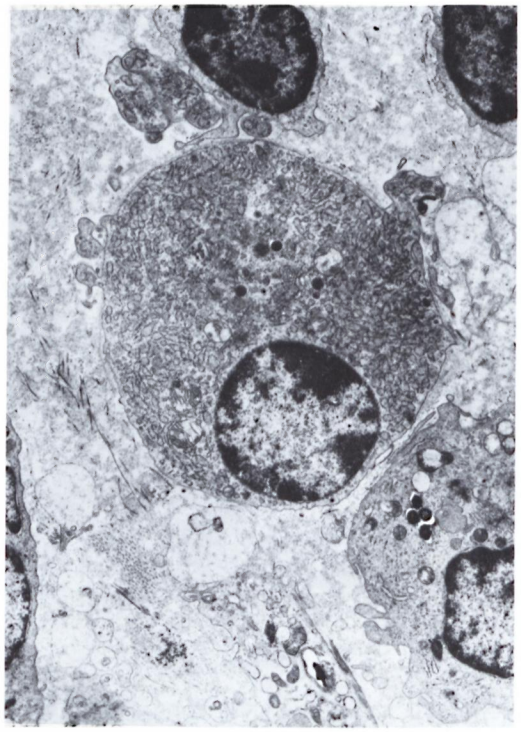

FIG. 5. Plasmacytoid cells were found among bacteria containing macrophages. These cells have abundant endoplasmic reticulum. Dense bodies and mitochondria are present. No bacilli were found in them. (×8000)

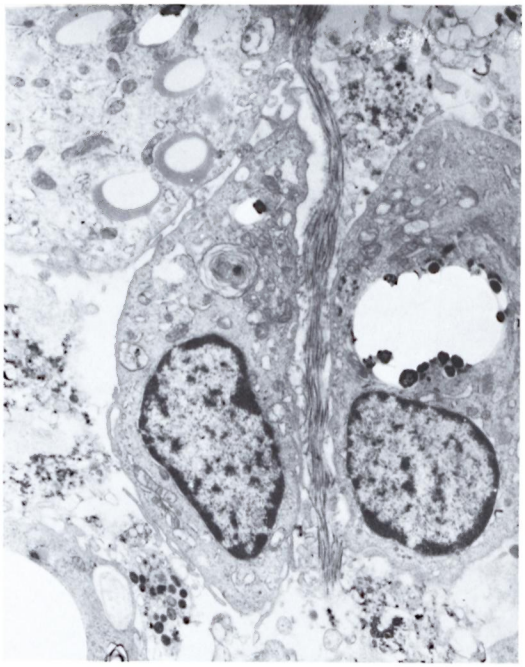

FIG. 6. Typical spindle shaped macrophages filled with bacteria and myelin bodies. Collagen fibrils are pronounced. These cells occupy the pseudocapsular area. (×8000)

sections passed down through the nodule from its periphery. The shape of the cell, though not the type, varied in each case, and it would seem that one possible source of confusion over the true identity of the main cell type in a histoid lesion might depend on the area being examined. It may also be true to say that the case described here represented a very active nodule of the histoid type and that it is possible that in older nodules, cells of the spindle type, seen in the pseudocapsular area, may predominate. The illustrations of Job, *et al.* [3] are all of this type, which led these authors to confer fibroblastic properties on histoid cells.

The main histoid cell type in this study was a young, not well differentiated, cell of the mononuclear phagocyte series. It contained few organelles or other signs of activation and none of the filamentous membraneous processes found in the macrophages of other forms of lepromatous leprosy [8]. With maturation the cytoplasm increased, but the character of the cell did not alter. No mitoses were seen, but many cells showed degenerative changes indicative of cell death without any accumulation of fat or foam. These findings coupled with the great cellularity of histoid nodules signify a very active macrophage granuloma in which the cells are relatively short-lived and turning over rapidly [9]. The dense granularity of nuclei was typical of high turnover cells; and plasmacytoid cells [4], which were found among the macrophages, have so far been described only in high turnover granulomas. It would appear, therefore, that histoid macrophages are stimulated as regards proliferation but without enhancement of functional activation. Thus the histoid lesion is a hyperactive form of lepromatous leprosy.

Although histoid lesions are found most commonly in relapsing patients, whether or not the relapse is due to drug resistance, this is not necessarily the case, and the stimulus that produces the high cell turnover has not been elucidated. It would appear to come from the active multiplication of bacilli in young cells in the early phase

of development of the nodule. In any case, the bacteriological activity (in most cases), the high cell turnover, and the lack of foamy change are clearly interlinked.

SUMMARY

A young active histoid nodule from an untreated patient with lepromatous leprosy was examined by electron microscopy. The only area where spindle-shaped cells predominated was near the pseudocapsule, and these cells were the only ones that were associated with the presence of collagen. The main mass of the granuloma was composed of young macrophages which showed evidence of a higher cell turnover rate than in ordinary lepromatous leprosy. Among the macrophages were plasmacytoid cells. Histoid lesions are thought to be essentially hyperactive, but the nature of the stimulus is unknown.

RESÚMEN

Se examinó al microscópio electrónico, un nódulo histoide jóven y activo proviniente de un paciente con lepra lepromatosa sin tratamiento. La única región donde predominaron células con aspecto de huso (alargadas) fue aquella cercana a la pseudocápsula y estas células fueron las únicas que estuvieron asociadas con la presencia de colágena. La masa principal del granuloma estuvo compuesta por macrófagos jóvenes los cuales mostraron evidencias de un intercambio celular más rápido que el observado en la lepra lepromatosa ordinaria. Entre los macrófagos se encontraron también células plasmacitoides. Las lesiones histoides se consideran esencialmente como hiperactivas pero se desconoce la naturaleza de su estímulo.

RÉSUMÉ

Un jeune nodule histoïde actif, obtenu chez un patient atteint de lèpre lépromateuse non traitée, a été examiné par microscopie électronique. La seule zone où prédominaient des cellules fusiformes, se trouvait près de la pseudo-capsule et ces cellules étaient associées à la présence de collagène. La masse principale du granulome était composée de jeunes macrophages qui témoignaient d'un taux plus élevé de remplacement des cellules que celui que l'on observe dans la lèpre lépromateuse ordinaire. On a relevé la présence, parmi les macrophages, de cellules plasmacytoïdes. On considère que les lésions histoïdes sont essentiellement hyperactives, mais la nature du stimulus est inconnue.

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REFERENCES

1. Desikan, K. V. and Iyer, C. G. S. Histoid variety of lepromatous leprosy. A histopathologic study. Int. J. Lepr. **40** (1972) 149–156.
2. Humphrey, C. D. and Pittman, F. E. A simple methylene blue azur basic fuchsin stain for epoxy-embedded tissue sections. Stain Technol. **49** (1974) 1.
3. Job, C. K., Chacko, C. J. G. and Taylor, P. M. Electron microscopic study of histoid leprosy with special reference to its histogenesis. Lepr. India. **49** (1977) 467–471.
4. Mokhtar, N. M. and Spector, W. G. Facsimile epithelioid cells obtained from stimulated peritoneal macrophages and their secretory activity *in vitro*. J. Pathol. **128** (1979) 117–126.
5. Pettit, J. H. S., Rees, R. J. W. and Ridley, D. S. Studies on sulfone resistance in leprosy. Int. J. Lepr. **34** (1966) 375–390.
6. Ridley, D. S. A skin biopsy study of lepromatous leprosy in relapse. Papua New Guinea Med. J. **16** (1973) 100–104.
7. Ridley, D. S. Skin biopsy in leprosy. Basel: Documenta Geigy. (1977).
8. Ridley M. J., Badenoch-Jones, P. B. and Turk, J. L. Ultra-structure of the mononuclear phagocyte series across the spectrum of leprosy. J. Pathol. (1980) in press.
9. Rodriguez, J. N. The histoid leproma. Its characteristics and significance. Int. J. Lepr. **37** (1969) 1–21.
10. Wade, H. W. The histoid variety of lepromatous leprosy. Int. J. Lepr. **31** (1963) 129–142.