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Histopathologic Reactions Following Intracutaneous Inoculation of *M. intracellulare* Serotype Davis [1]

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The histogenesis and structure of the tubercle after infection with *M. tuberculosis* and *M. bovis* are well known ([6, 17, 18, 30-32]). A great deal of work has also been done on the histopathology of leprosy ([7-11, 16, 29]). A large group of potentially pathogenic mycobacteria, especially *M. intracellulare-M. avium* complex, are of great clinical and bacteriologic interest ([1, 2, 4, 5, 12, 33, 34]). The infective potentiality of these so-called "atypical mycobacteria" is not fully understood although the pathogenicity of many of these mycobacteria is appreciated and their identification is accomplished ([3, 5, 12, 15, 25, 26, 35]). Comparative histopathologic studies with different groups of potentially pathogenic mycobacteria are rare and the results are variable and contradictory ([3, 13-15, 21, 23, 25-27, 36]). In previous experiments with rabbits, guinea pigs, chickens and mice, we have studied the pathogenicity and virulence of a strain of Group III (Runyon) mycobacterium, *M. intracellulare* serotype Davis ([19, 21, 24, 28]). The strain was found locally pathogenic with a low virulence. After different routes of inoculations with different doses, localized abscess formation was found. Repeated oral infection was unsuccessful. Localized abscess formations with tuberculous-like granulomas in internal organs were seen in some animals. A generalized tuberculous-type inflammation was never found.

Further comparative histopathologic examinations were done with living and dead mycobacteria of the same strain on local tissue reactions of the skin. These examinations of the dermal lesions after infection with *M. intracellulare* were performed in order to study the response to mycobacterial infections of the skin other than that due to *M. tuberculosis* with special emphasis on the peculiar response of leprosy bacilli to man.

MATERIALS AND METHODS

Bacillary strain. A laboratory strain of *M. intracellulare* serotype Davis (ATCC 23435) was cultured on Gottsacker egg medium. Fresh culture material after cultivation of 10 to 14 days was used for inoculation ([19, 24]).

Animals. "Yellow-silver" rabbits with a mean weight of 2,000–2,500 gm, "pearl-white" guinea pigs with a mean weight of 400 gm, and white mice with a mean weight of 50 gm were used. Guinea pigs and mice were bred and kept mycobacteria-free. With rabbits this was not possible ([20]).

Inoculation. *Using living mycobacteria.* Different doses (5 mg, 10 mg, 50 mg) of fresh mycobacteria cultured on Gottsacker egg medium were dissolved in a suspension of 0.9% NaCl solution, and 0.1 ml (respectively 0.2 ml for 50 mg) was injected intracutaneously in the neck of guinea pigs and rabbits and in the foot pads of mice.

Using dead mycobacteria. A suspension of heat-killed mycobacteria of the same strain was dissolved in phenol: 10 mg of the mycobacteria dissolved in 0.1 ml was injected in the neck of guinea pigs and rabbits.

Course of the experiment. The infected animals were examined weekly and a group of animals were killed at weekly intervals. The inflamed tissue of the neck was excised together with the surrounding skin. During autopsy, specimens of liver, spleen, lungs and kidneys were taken. Serial paraffin and frozen sections were made. The following stains were used: hematoxylin-eosin, Ziehl-Neelsen stain with methylene blue and malachite green.

RESULTS

Histopathologic findings. *Inoculation of living mycobacteria; rabbits and guinea pigs.* The tissue reactions after intracutaneous in-

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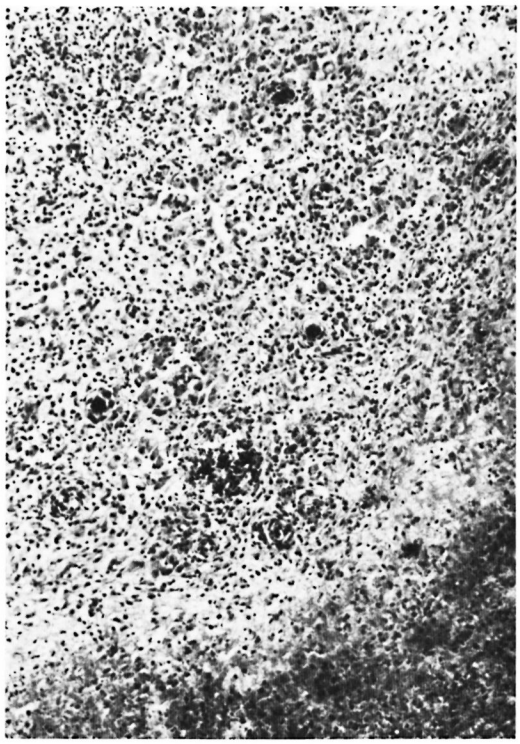

FIG. 1. Skin of a rabbit three weeks after intracutaneous infection with living mycobacteria. Necrosis of degenerating leukocytes is seen on the right side and next to this a granuloma consisting of leukocytes, macrophages, immature epithelioid cells, lymphocytes and a few plasma cells. ×80.

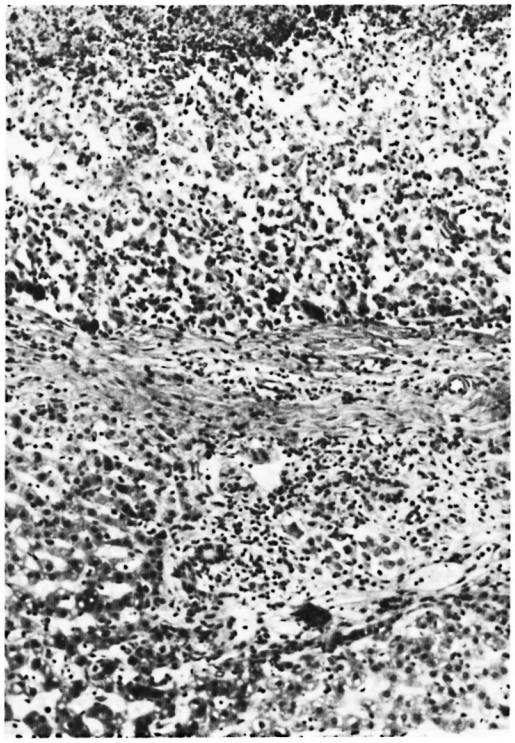

FIG. 2. Liver of a guinea pig after intracutaneous infection with living mycobacteria. Abscess formation with a central necrosis on the left side, surrounded by immature epithelioid cells, separated by edema, forming an epithelioid granuloma. The abscess is demarcated from the liver tissue by a fibrous capsule and a wall of scanty lymphocytes. ×80.

fection of rabbits and guinea pigs were similar. In the first week a reddish brown nodule appeared. The overlying skin was damaged by a localized abscess and yellowish pus discharged. Numerous AFB could be seen in this pus. Skin ulcers appeared with sharp margins and a hemorrhagic floor. The healing process began in the third week with a fibrinous coat and the formation of a granuloma. Histopathologic examination in the first week showed an acute exudative inflammatory reaction with predominant polymorphonuclear neutrophils and only a few mononuclear cells. The abscess formation with necrosis of the upper layer of the skin was localized. The infiltration involved the whole skin thickness to the subcutaneous fat. A large number of intact AFB were demonstrated in the zone of degenerating leukocytes and in the fibrinous necrosis, most of the mycobacteria being arranged in clumps.

In the second and third weeks, macrophages, lymphocytes, plasma cells and fibroblasts infiltrated from the surrounding tissues. Most of the macrophages had abundant cytoplasm, a round, oval or reniform nucleus and phagocytic vacuoles. Normal AFB and amorphous material was phagocytized by polymorphonuclear leukocytes and macrophages. A granuloma was formed around the zone of necrosis in the dermal layer and about the margins of the ulcer of the epidermis. In the granuloma an increasing number of large pale cells with cloudy cytoplasm and elongated pale nuclei appeared. These cells resembled epithelioid cells but did not correspond in size and characteristic features with mature epithelioid cells. These immature epithelioid cells were sometimes separated by edema. Some of these immature epithelioid cells were arranged in a palisade manner, forming a sparse granuloma around

the zone of necrosis. A homogeneous caseous center was not seen. A few multinucleated Langhans giant cells and foreign body giant cells were also seen. The nuclei of the Langhans giant cells were arranged in a horseshoe pattern. In the deeper layer of the skin perivascular infiltrations were found which consisted chiefly of leukocytes and some lymphocytes.

After four weeks, the epithelioid granuloma was fully developed with proliferating capillaries and fibroblasts. Most of the skin ulcers were healed after five to six weeks. In none of the sections were the characteristic features of a tubercle found. Only a few intact AFB were demonstrated in the epithelioid granuloma, mostly in the zone of necrosis; some were free and others were ingested by macrophages, leukocytes and few by immature epithelioid cells. Similar findings were seen in the internal organs, except for the lungs. In the lungs of the rabbit, a leukocytic inflammation was sometimes found without granulomas. Some of the guinea pigs died during the process of the experiment and the lungs showed a leukocytic and hemorrhagic pneumonia. Bacteriologic examinations demonstrated a bacterial pneumonia mostly caused by hemophilus and coliform bacteria, but not by mycobacteria. Localized abscess formations were seen in the liver, spleen and kidney consisting of a zone of necrotic leukocytes, surrounded by a scanty granuloma consisting of immature epithelioid cells, macrophages, a few multinucleated Langhans giant cells and lymphocytes. Sometimes the lymphocytes formed a wall. The abscesses were demarcated from the normal surrounding tissue by a fibrinous capsule. Only a few AFB were demonstrated in these abscesses.

Inoculation of living bacilli; mouse foot pads. A different variety of inflammation was found in the mouse foot pad. There was intensive diffuse leukocytic inflammation with fibrinoid necrosis, edema and suppuration. The skin was macerated with necrosis of the toes. The leukocytic inflammation per-

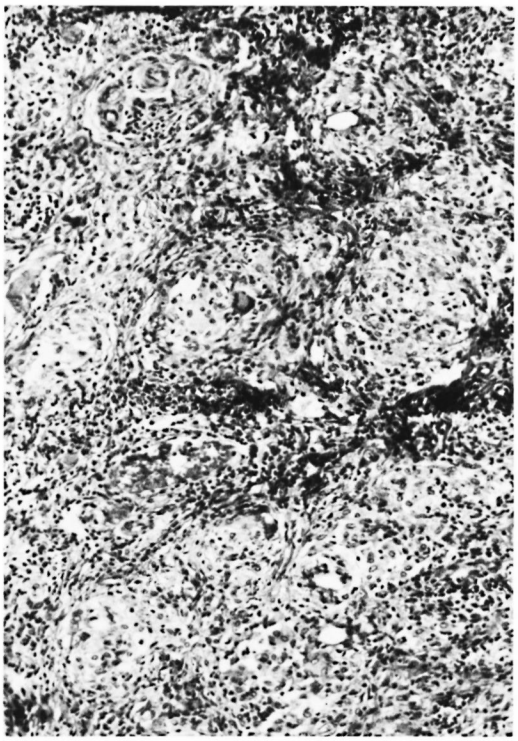

FIG. 3. Skin of a guinea pig four weeks after inoculation of heat-killed mycobacteria. Granuloma consisting of mature epithelioid cells, lymphocytes and multinucleated giants cells. ×80.

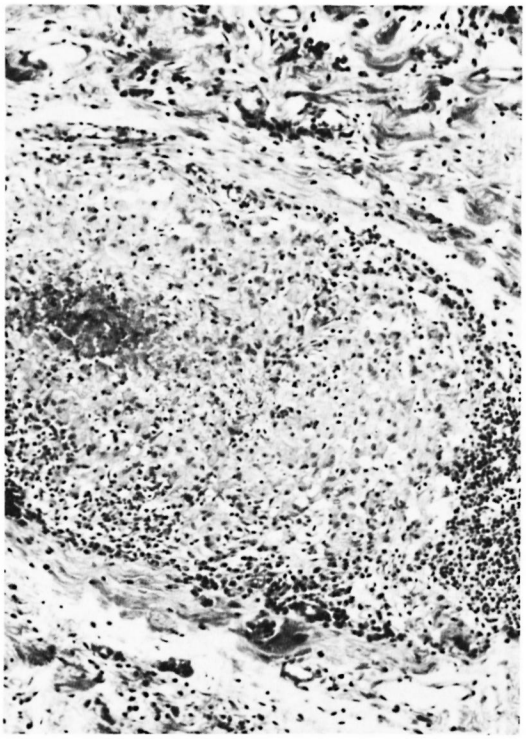

FIG. 4. Skin of a rabbit three weeks after inoculation of heat-killed mycobacteria. Epithelioid granuloma consisting of a central necrosis, surrounded by a layer of mature epithelioid cells and an outer wall of lymphocytes. ×80.

sisted for five weeks. During this time a histoid granuloma was formed but no epithelioid cells and giant cells were seen. Numerous AFB were observed up to five and six weeks. This inflammation and the histoid granuloma were quite different from a tuberculous granuloma.

After inoculation of heat-killed mycobacteria. A suspension of heat-killed mycobacteria of the same strain was injected intracutaneously in the neck of rabbits and guinea pigs. After an initial leukocytic inflammation in the first week, a granuloma developed in the second and third weeks which consisted of macrophages, lymphocytes, fibroblasts and an increasing number of large polygonal cells with elongated pale nuclei and abundantly cloudy cytoplasm. These cells were most likely mature epithelioid cells. The epithelioid cells were arranged in a palisade manner around a central zone of necrosis, forming a tuberculoid granuloma. Multinucleated Langhans giant cells and a few foreign body giant cells were seen. Sometimes a wall of scanty lymphocytes was observed.

After five to six weeks the localized ulcers of the skin healed. The macroscopic appearance of these ulcers were similar to those seen after inoculation of living mycobacteria. A large number of solid staining and granulated AFB were seen in the first week; later on the number of solid staining mycobacteria quickly diminished. Most of them were ingested by macrophages. This granulation reaction resembled a tuberculoid granuloma or an epithelioid granuloma after inoculation of complete Freund's adjuvant.

DISCUSSION

A comparison with previous animal experiments utilizing *M. intracellulare* serotype Davis showed differing results. Inoculation of the same strain ATCC 23435 caused: a) in man, a chronic tuberculous-type granuloma ([22]); b) in chickens, tuberculoid granulomas or the Yersin type of septic reaction ([21]); c) in rabbits and guinea pigs, abscess formations with an epithelioid granuloma consisting of immature epithelioid cells and giant cells; and d) in the mouse foot pad, a leukocytic inflammation with suppuration and a histoid granuloma.

In none of the examined animals were there seen typical tuberculous-type granulomas. The tissue reaction after inoculation of living mycobacteria showed an exudative type of inflammation and an epithelioid granuloma corresponding with the character of a high-turnover granuloma ([37]). The intensity of the tissue reactions and the degree of inflammation was independent of the number of inoculated mycobacteria. On the other hand, a tuberculoid granuloma developed after intracutaneous injection of killed mycobacteria, consisting of fully mature epithelioid cells, multinucleated giant cells and lymphocytes. The reaction to living mycobacteria was suggestive of a pyogenic infection with the accumulation of leukocytes, the discharge of pus and intensive exudation. The reduction of the bacterial load, the constant arrival of new macrophages, and the development of giant cells and immature epithelioid cells resembled a hypersensitivity granuloma ([37]). The various histopathologic reactions in man and different animals might be explained by differing interaction with the infected host and differing immune response. The components inducing these specific responses are not known. This type of inflammation is localized between the polar types of pyogenic inflammation and the tuberculous type of granuloma.

The different tissue reactions in the same host after inoculation of living and dead mycobacteria of the same strain might be caused by metabolic and toxic processes of living mycobacteria with a different activation of the monocyte-macrophage system. It is not well understood why there is no transformation of macrophages to fully mature epithelioid cells, but instead immature epithelioid cells without the characteristic features of a tuberculous-type granuloma. Additional studies with different sensitin tests on mycobacteria-free guinea pigs demonstrated a delayed-type skin reaction with declining reactions to homologous and heterologous sensitins six weeks after intradermal inoculation with the same strain (unpublished data).

These findings can be explained by the self-limited nature of the inflammation due to local pathogenicity. The low activation of the monocyte-macrophage system with incomplete epithelioidization of macrophages is not explained. More comparative histopathologic examinations with different groups of potentially pathogenic mycobac-

teria should be done to explain the different histopathologic reactions of mycobacterial infections. This different pathologic response after intradermal infection with *M. intracellulare* serotype Davis may explain why alternative experimental models with potentially pathogenic mycobacteria are of little value in experimental leprosy research.

SUMMARY

A locally pathogenic and low virulence strain of *M. intracellulare* serotype Davis (ATCC 23435) was used to compare the local inflammation of skin and its histopathologic changes in rabbits, guinea pigs and mouse foot pads after intracutaneous inoculation of living and dead mycobacteria. In rabbits and guinea pigs, after injection of living mycobacteria, localized abscess formations were found. Weekly histopathologic examinations of the skin showed an intensive leukocytic inflammation in the first week, followed by an epithelioid granuloma consisting of immature epithelioid cells, macrophages, Langhans giant cells, foreign body giant cells and lymphocytes. A tuberculoid granuloma was sometimes observed without the characteristic feature of a tubercle. In the short-lived lesions, fully mature epithelioid cells could not be seen. After intracutaneous inoculation of heat-killed mycobacteria of the same strain, abscess formation occurred in the skin. First a leukocytic inflammation was seen, followed by a tuberculoid granuloma consisting of mature epithelioid cells, lymphocytes, Langhans giant cells and foreign body giant cells. The foot pad infection of the mouse was localized with an intensive leukocytic inflammation and suppuration. A histoid granuloma was seen which was quite different from a tuberculous granuloma. It is not well understood why the same strain in man, chickens, guinea pigs and mice caused different histopathologic reactions without forming a typical chronic tuberculous-type of inflammation, but initiated instead a pseudogranulomatous tissue reaction with immature epithelioid cells and a nontuberculous epithelioid granuloma.

RESUMEN

Se usó una cepa del *M. intracellulare,* localmente patogénica y de baja virulencia (serotipo Davis, ATCC 23435), para estudiar y comparar la inflamación local de la piel y sus cambios histopatológicos en conejos, cobayos y cojinetes plantares del ratón, después de la inoculación intracutánea de las micobacterias vivas o muertas.

En los conejos y cobayos, se observó la formación de abscesos localizados después de la inyección de las micobacterias vivas. El examen histopatológico semanal de la piel, mostró una inflamación leucocítica intensa en la primer semana, seguida por un granuloma formado por células epitelioides inmaduras, macrófagos, células gigantes de Langhans, células gigantes de "cuerpo extraño" y linfocitos. Algunas veces se observó un granuloma tuberculoide sin las características morfológicas de un tubérculo. No se pudieron observar células epitelioides plenamente maduras en las lesiones de vida-media corta. La inoculación intracutánea de la misma cepa micobacteriana muerta por calor, condujo a la formación de abscesos en la piel. Primero se observó un infiltrado inflamatorio leucocítico seguido por un granuloma tuberculoide formado por células epitelioides maduras, linfocitos, células de Langhans y células gigantes "de cuerpo extraño." La inoculación en el cojinete plantar del ratón, originó una infección localizada con intensa inflamación leucocítica y supuración. Se observó un granuloma histioide completamente diferente del granuloma tuberculoso. No está bien claro cómo es que la misma cepa micobacteriana causa diferentes reacciones histopatológicas en el hombre, pollos, cobayos y ratones, sin formar una típica inflamación crónica del tipo tuberculoso. La inflamación se inicia, en cambio, con una reacción tisular pseudogranulomatosa con células epitelioides inmaduras y por un granuloma epiteliode no tuberculoso.

RÉSUMÉ

On a utilisé une souche de *M. intracellulare* sérotype Davis (ATCC 23435) de faible virulence et à caractère pathogénique localisé, pour comparer l'inflammation locale de la peau à la suite de l'inoculation intra-cutanée de mycobactéries vivantes et mortes ainsi que les modifications histo-pathologiques qui en résultent chez les lapins, les cobayes et dans le coussinet plantaire de la souris. Chez les lapins et chez les cobayes, on a observé la formation d'abcès localisés après injection de mycobactéries vivantes. L'examen histo-pathologique de la peau pratiqué à intervalle hebdomadaire a montré une inflammation intense à leucocytes au cours de la première semaine, suivie pas la formation d'un granulome épithélioïde consistant de cellules épithélioïdes immatures, de macrophages, de cellules géantes de Langhans, de cellules géantes à corps étrangers et de lympho-

cytes. Un granulome tuberculoïde a parfois été observé, sans qu'il présente cependant les caractéristiques d'un tubercle. Dans les lésions de courte durée, il n'a pas été possible de mettre en évidence des cellules épithélioïdes ayant achevé leur maturité. Après inoculation intra-cutanée de mycobactéries tuées par la chaleur, appartenant à la même souche, on a vu apparaître la formation d'abcès dans la peau. Tout d'abôrd, une inflammation leucocytaire a été observée, suivie d'un granulome tuberculoïde consistant de cellules épithélioïdes matures, de lymphocytes, de cellules géantes de Langhans, et de cellules à corps étrangers. L'infection du coussinet plantaire de la souris était localisée, avec inflammation leucocytaire accusée et suppuration. Un granulome histoïde a été observé, avec des caractéristiques absolument différentes de celles du granulome tuberculeux. On ne comprend pas bien pourquoi la même souche produit des réactions histo-pathologiques différentes chez l'homme, le poulet, le cobaye et la souris, sans développement d'inflammation chronique typique du type tuberculeux, mais commençant au contraire comme une réaction tissulaire pseudogranulomateuse avec cellules épithélioïdes immatures et formation d'un granulome épithélioïde d'aspect non tuberculeux.

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