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Leukoderma syphiliticum: Ultrastructural Observations on Melanocyte Function

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Abstract. A case of genital leukoderma syphiliticum was analysed submicrospically. No treponema pallidum organisms could be detected intra- or extracellularly in the epidermis or in the dermis. The melanocytes were only slightly reduced in number and had mostly normal outlines. The melanogenesis was impaired and small melanosomes with decreased deposition of melanin were mostly produced at the expense of normal melanin granules. A partial block in the melanin transfer mechanism seems to be in evidence. As no direct destructive action of spirochetes on the melanocytes is observed, an indirect effect is assumed, e.g. by a tyrosinase inhibitor.

Key words: Lues; Melanosomes; Pigmentation

Leukoderma has been known since ancient times as a classical syphilitic stigma. Nowadays this sign is infrequently observed and occasional reports concern uncommon localizations (6). Leukoderma syphiliticum (LS) develops during the resolution of a roseol or papular syphilis and often persists throughout life. The occurrence of treponema pallidum in other, secondary lesions such as roseol, papules, and condyloma lata has long been well known. The exact localization in the various lesions of the spirochetes intra- and extracellularly has recently been classified by electron microscopic investigations (4, 8, 9). However, in the cases of LS, it is not known if treponema pallidum produces its effect upon the melanocytes via a destructive action or by an inhibitory effect. To clarify this, electron microscopic analyses were performed in one case of LS. This case was the first one in a large material of syphilitic patients observed for many years and is furthermore unusual in its localization.

MATERIAL

The patient was a 24-year-old male homosexual who presented asymptomatic macular hypopigmentations of penis and scrotum (Fig. 1*a, b*). He was in good health and a routine serology check-up one year ago proved negative. Anamnestic data indicated that primary sclerosis preceded the pigment changes by 2 months.

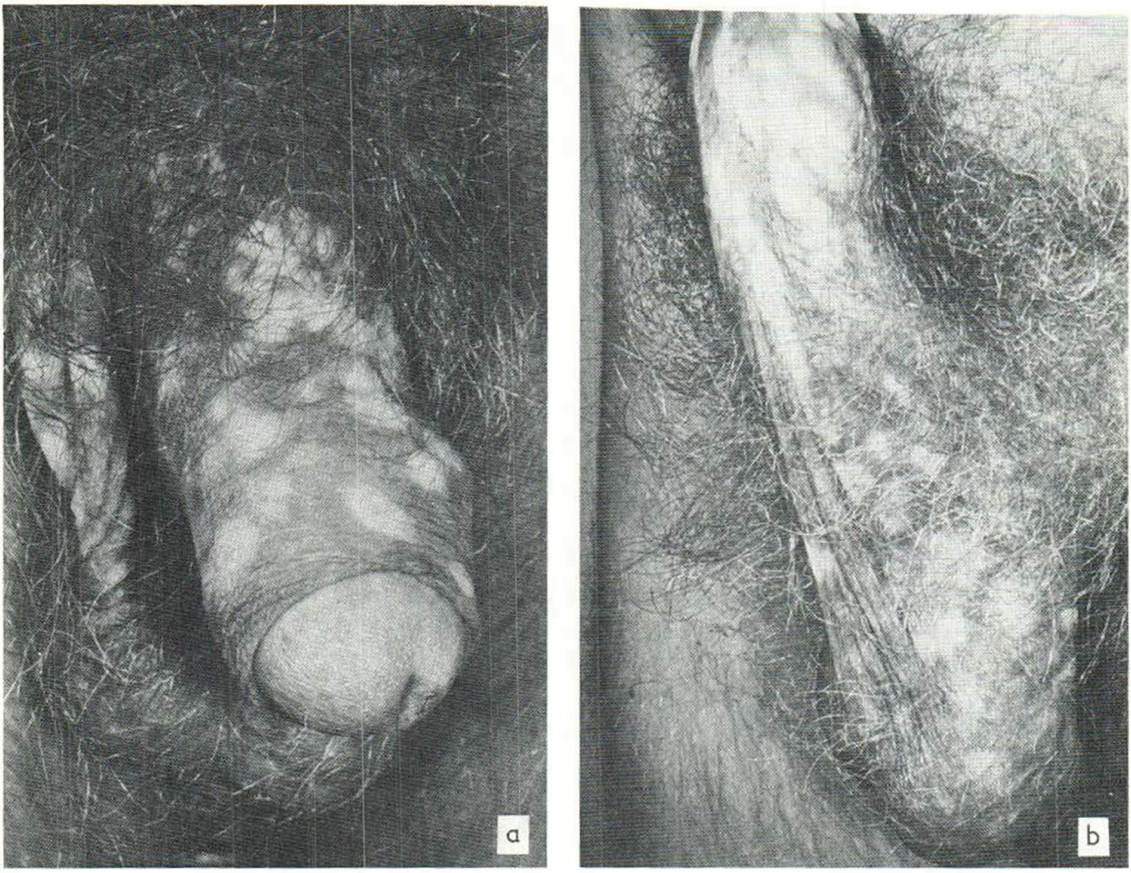

Fig. 1 a and b. Clinical appearance of the patient.

The skin changes were obvious, depigmented areas up to 2 cm diameter were seen, and the surrounding genital skin seemed hyperpigmentated. Inguinal and axillary lymph nodes were enlarged. Serological tests revealed strongly positive Wassermann reaction, a positive FTA-abs and TPI. According to the serological findings and anamnestic information, it was judged that he had an early stage II syphilis.

Treatment was given (Swedish standard) with 600 000 IE procain-penicillin i.m. for 17 days. The serology was checked regularly and after 2 years the Wassermann reaction turned negative, while FTA-abs and TPI remained positive. During the observation time the hypopigmentations showed no changes whatsoever.

METHODS

Punch biopsies were obtained from depigmented and pigmented areas. Specimens were processed for routine histological examination and Warthin-Starry's staining for spirochetes. Material for electron microscopy was fixed in 2% glutaraldehyde buffered with a phosphate solution at pH 7 for 6 hours at 4°C. Post-fixation was performed in 2% osmium tetroxide buffered with the phosphate solution for 2 hours at 18°C. The specimens were rinsed in the phosphate solution and dehydrated in increasing concentrations of acetone. The specimens were embedded in Spurr and ultrathin sections double-stained with uranyl acetate and lead citrate.

RESULTS

Light microscopy

The hematoxylin and eosin stained sections revealed an absence of pigmentation but an otherwise normal histological picture, in comparison to the heavily pigmented normal skin. No spirochetes were observed in the Warthin-Starry stained sections.

Electron microscopy

Sections from perilesional specimens showed a normal organization of both epidermis and dermis.

In areas of depigmentation no pathological changes were found in the blood vessels. The sub-

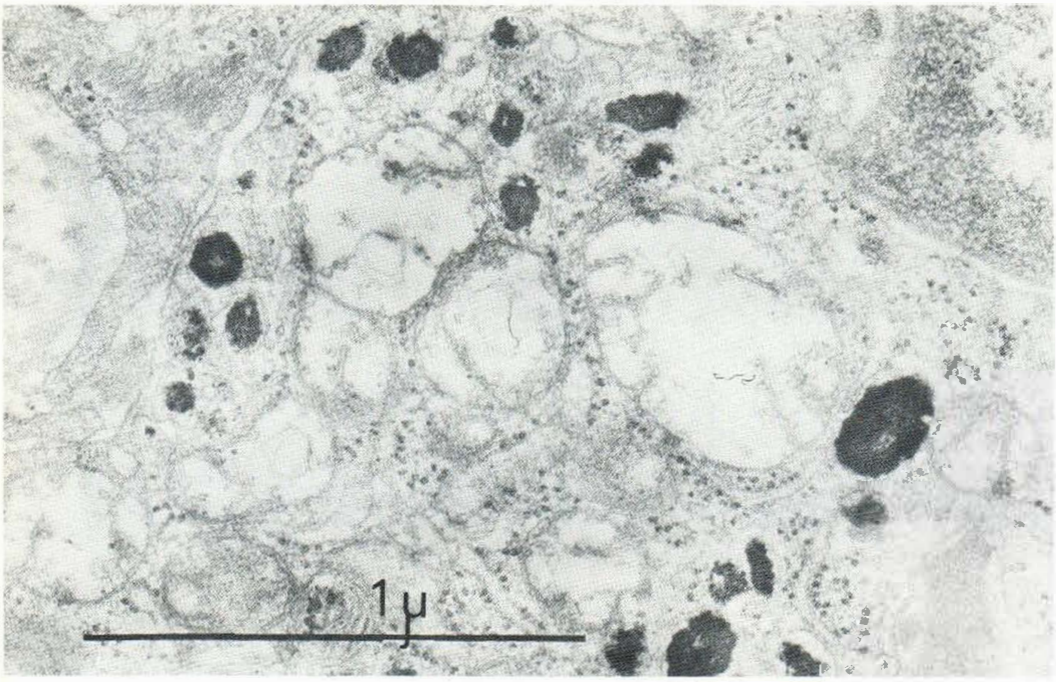

Fig. 2. Cytoplasm of melanocyte containing melanosomes and swollen mitochondria. ×66000.

structure of the fibrillar and cellular parts of the dermis was normal. No structures indicating an occurrence of spirochetes were observed.

The lamina basalis and the structural layering of the epidermis were normal. Melanocytes were reduced in number, although not excessively so. There was no enlargement of the population of Langerhans' cells. The outline of the melanocytes was generally normal, although shrunken and degenerated melanocytes occasionally occurred. The dendritic nature of the melanocytes was well preserved. In the cytoplasm, melanosomes were uniformly distributed in a normal or moderately reduced number. There was a paucity of fully melanized melanosomes of stage IV. The bulk of the melanosomes were reduced in size and were more or less incompletely melanized. Aberrant outlines of the melanosomes were frequently observed. There was a conspicuous lack of melanosomes in the dendritic processes (Fig. 2).

Melanosome destruction within lysosomes was only occasionally observed. The Golgi apparatuses were poorly differentiated and the endoplasmic reticulum often appeared dilated. Mitochondria of many melanocytes showed loss of cristae, swelling, and vacuolation. The nucleus exhibited no pathological changes.

The cytoplasm of adjacent keratinocytes contained a sparse population of melanin granules, singly distributed and more or less disintegrated. The substructural organization of the keratinocytes was otherwise normal (Fig. 3).

DISCUSSION

Leukoderma syphiliticum is a well-known manifestation of infection by treponema pallidum. However, the mechanism of this depigmentation and factors triggering the reaction have not been clarified. A direct action of treponemes on the melanocytes has earlier been claimed as eliciting this phenomenon.

Treponema pallidum has been recovered in various secondary lesions of syphilis, both intracellularly and extracellularly (4, 8, 9).

However, thorough analyses of the present material have not rendered it possible to demonstrate any signs of *Treponema pallidum* in any kind of epidermal cells or in the dermis. This of course does not exclude a precious occurrence of spirochetes in

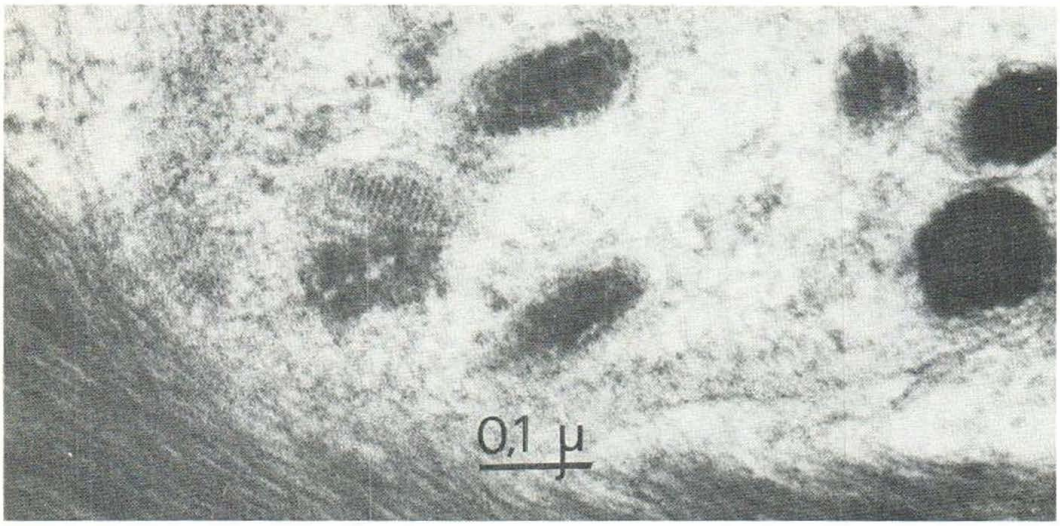

Fig. 3. Occurrence of early stages of melanosomes in cytoplasm of keratinocyte. ×144000.

the epidermis during the early developmental phases of LS, especially when LS develops from a roseal or papular syphilis. A direct and destructive effect of the spirochete on the melanocyte is yet not present, as melanocytes are only slightly reduced in number and exhibit a certain melanin synthesis. The depigmentation of LS appears to be caused by a disturbance of the melanocyte function. Melanogenesis can apparently take place despite minor changes in the endoplasmic reticulum such as dilatation as well as cristolysis and swelling of the mitochondria, although these reactions are sensitive indicators of melanocyte morbidity. However, the final outcome of the melanin synthesis is a product of small and incompletely melanized melanosomes and there is a partial block in the transfer of melanin granules to keratinocytes with an obvious lack of even dispersion of melanin throughout the keratinocytes of the epidermis. Within the cytoplasm of keratinocytes there was no prevailing formation of lysomal destruction of melanosomes, even though their size is small—thus facilitating such a process. Hence no further contribution to the depigmentation was obtained by such a process.

On the basis of these observations an indirect influence of the spirochetes on the melanocytes seems plausible, but by what means this action is effected is obscure. Other authors studying hypopigmented lesions in infectious diseases, such as leprosy and pityriasis versicolor as well as sarcoidosis (1, 2, 3), have observed degenerative changes, partly blocked functions and depressed melanogenesis. *M. leprae* possesses an enzyme, *o*-diphenol oxidase, which oxidizes dopa, and Prabhakaran et al. (7) have suggested that utilization of dopa by *M. leprae* causes the hypopigmentation. However, in the ultrastructural study of Job et al. (3) no *M. leprae* was found in melanocytes and as in this type of lepra, bacillae are not ordinarily demonstrated, an enzyme effect is improbable. The depigmentation by colonization of the stratum corneum by *Pityrosporum orbiculare* is claimed to be due to tyrosinase inhibitors with a melanocytotoxic effect, as C_9 and C_{11} dicarboxylic acids are capable of inhibiting the dopa-tyrosinase reaction in vitro (5). Whether *Treponema pallidum* contains a tyrosinase inhibitor and a dopa oxidative enzyme is not yet known, but it would appear likely.

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Sensitization to Cobalt Associated with Nickel Allergy: Clinical and Statistical Studies

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Abstract. In 76 cases (5.8%) of a population of 1 310 cases (examined by patch tests for possible contact dermatitis) a combined (coupled) allergy was found to nickel and cobalt. In 37 out of the 76 cases this combined allergy was associated with clinical dermatitis of the hands. Statistical chi-square analysis revealed that in the original population of patients examined, apart from a strong association between nickel and cobalt reactions, a significant association was also seen extending to the actual level (weakly to strongly positive) of reactions. Moreover this statistically significant association was still seen within the restricted population of combined nickel and cobalt allergics. Statistical association within the population of combined nickel and cobalt allergy between the strength of the Ni and Co reactions and positive reactions to other antigens of routine ICDRG-standard battery was not encountered, however. Positive reactions to cobalt were rare, but extreme. Nickel patients appeared to have about 50 times greater odds of being extreme cobalt positive. The possibility is discussed that facilitation of clinical cobalt allergy might be triggered by a high grade of nickel sensitivity.

Key words: Cobalt hypersensitivity; Nickel hypersensitivity; Coupled hypersensitivity; Statistical investigations

Combined cobalt (Co) and nickel (Ni) allergy is considered to be due to independent sensitization and not to cross-sensitivity (11). This phenomenon has been discussed by several authors (2, 8, 1). In this study 1 310 patients suspected of having allergic contact dermatitis were subjected to patch test procedures in the period 1977–80. In total 211 cases of sensitization to Co, to Ni or to both metal allergens were found (Table I).

Although the interpretation of the rates of positivity by carefully performed epicutaneous tests revealed only a momentary restricted insight into the grade of hypersensitivity, in principle most in vitro tests have the same disadvantage. In this study of 211 individuals with Co and/or Ni allergy the rate of hypersensitivity to each one of the metals was statistically compared. In a selected group (76 cases, including 37 cases of dermatitis of the hands) of the previously described 211 cases, in a combined nickel and cobalt allergy was found, the same statistical study was performed.

MATERIALS AND METHODS

Patch tests were performed during the inactive phase of dermatitis using commerical (Trolab-Hellerup, Denmark) allergens ($NiSO_4$ 2.5% and $CoCl_2$ 1% in petrolatum according to the standardized procedures recommended by the International Contact Dermatitis Research Group (ICDRG) (6). Both metals (Ni and Co) were applied symmetrically on the right and the left side of the back respectively at a reliable distance from each other. Simultaneously the various other antigens of the adapted routine ICDRG standard battery (6) (Table VII) were tested. For patch testing, uniform standard patches (IMECO) (6) were used.

The results were read after 72 hours (24 hours after removal of the patches). The skin reactions were graded extreme (+++), strong (++), weak (+) or negative, as indicated in the literature (13) (Tables I–VI).

There are many ways of investigating the data statistically with regard to a possible positive association between Co and Ni allergy. One adequate way is by looking at various 2×2 tables formed by aggregation of certain patient categories, carrying out the chi-square test for association in such a table and computing the associated odds ratio.

RESULTS

A coupled Co and Ni allergy was found in 76 out of the 1310 cases (5.8%). For solitary cobalt and nic-