

GIANT MELANIN GRANULES IN VITILIGINOUS ACHROMIA WITH MALIGNANT MELANOMA

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Abstract. Histological and ultrastructural examination of normal and perilesional skin of a patient with vitiliginous depigmentation associated with a malignant melanoma revealed the presence of giant melanin granules in keratinocytes and melanocytes. These structures are compared to macromelanosomes which have been observed in numerous pigmentary diseases. The formation and significance of the giant melanin granules is discussed.

Key words: Vitiligo; Malignant melanoma; Melanin; Melanosomes

Giant melanin granules have been reported in various dermatoses including nevus spilus (3, 9, 10), melanocytic naevi (8, 13), eruptive naevi (4), generalized lentiginos and multiple lentiginosis syndrome (2, 12, 14), xeroderma pigmentosum (5), café-au-lait spots of neurofibromatosis (6), melanotic macules in Albright's syndrome (1), generalized melanosis due to metastatic melanoma (10) and even in normal skin of healthy individuals (8). They have also been observed in both the eye and skin in several patients with X-linked ocular albinism (11).

We have observed several giant melanin granules in the skin of a patient with vitiliginous depigmentation associated with a malignant melanoma, at the edge of a depigmented patch and in the normal surrounding skin.

MATERIAL AND METHODS

Case report. A 68-year-old woman presented with a malignant melanoma on the sole of the right foot in June 1971. The melanoma was excised in 1971. Between May '74 and March '75, she was treated with B. C. G. immunotherapy once a week. In April 1975, cutaneous and cerebral metastases appeared. Death occurred in October 1975. Achromia had begun in 1972 on the dorsa of the hands and on the forehead, and progressed slowly on the arms, trunk and limbs.

Electron microscopy. For electron microscopy, punch biopsies were taken from the centre of a 2-year-old

achromic lesion on the dorsum of the hand, from the edge of the lesion and from normal skin of the forearm. This material was fixed in 3% glutaraldehyde for 1 h, post-fixed in osmic acid for 1 h, dehydrated in graded alcohols, embedded in Epon and sectioned in a Reichert ultramicrotome. The sections were stained with Uranyl acetate and lead citrate and examined in a Hitachi HU 12 A electron microscope.

RESULTS

Semithin sections (Fig. 1a and b). The distribution of the melanin granules of the basal layer was irregular. Several round dense granules were observed, principally at the inferior pole of many of the cells of the basal layer. These granules were of similar optical density to melanin granules but much larger in size. In Fig. 1b, the arrowed giant melanosome seems to be a basal keratinocyte.

Electron microscopy. Giant spherical granules were observed in several epidermal melanocytes in the region of the border of the depigmented areas and in the normal skin some distance from the lesions (Fig. 2). These probably represent giant melanin granules. Their size (1.6–2.1 μm) is much greater than that of the normal melanosomes (0.3 $\times$ 0.1 μm) seen in this patient. In the stained sections, they appear homogenous. At very high magnification the granules were seen to consist of very fine particles in a narrow grouping. These fine particles are more clearly visible at the periphery of the giant granules.

In the middle of one of these giant granules rounded areas, slightly less electron dense, were seen. In one of them, there was only one clearer zone of diameter approximately 0.1 μm whereas the other showed several but of smaller size (3–500 Å). Although the contours of the giant granules were fairly well demarcated, they were not usually surrounded by a membrane. However a condensation of cytoplasmic microfilaments was present in

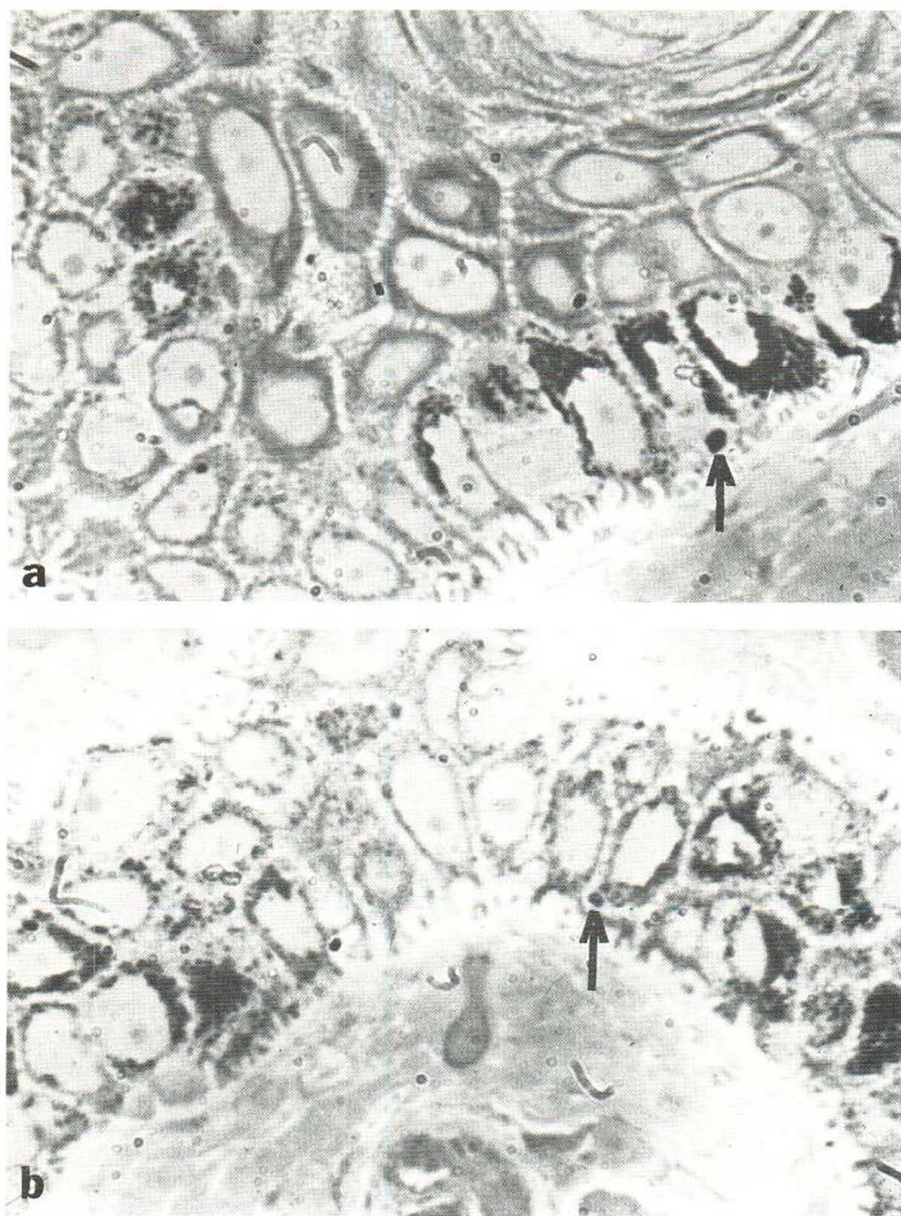


Fig. 1a and b. Giant melanin granules in basal cells ($\times 980$).

places at the periphery of the granules. The giant pigment granules usually occurred singly in a cell but we observed one melanocyte which contained two (Fig. 3). We did not observe granules in the dermal melanophages or in basal keratinocytes.

Several of the cells containing these giant melanin granules were identified as melanocytes by the absence of tonofilaments and desmosomes. More-

over the presence of a "disc plate" on the plasma membrane in relation to the basal membrane and neighbouring cells supports this conclusion. These melanocytes showed significant changes. The cytoplasm was retracted and the intercellular space much enlarged. Many mitochondria were swollen and the endoplasmic reticulum was very dilated. Numerous free ribosomes and a few microfilaments

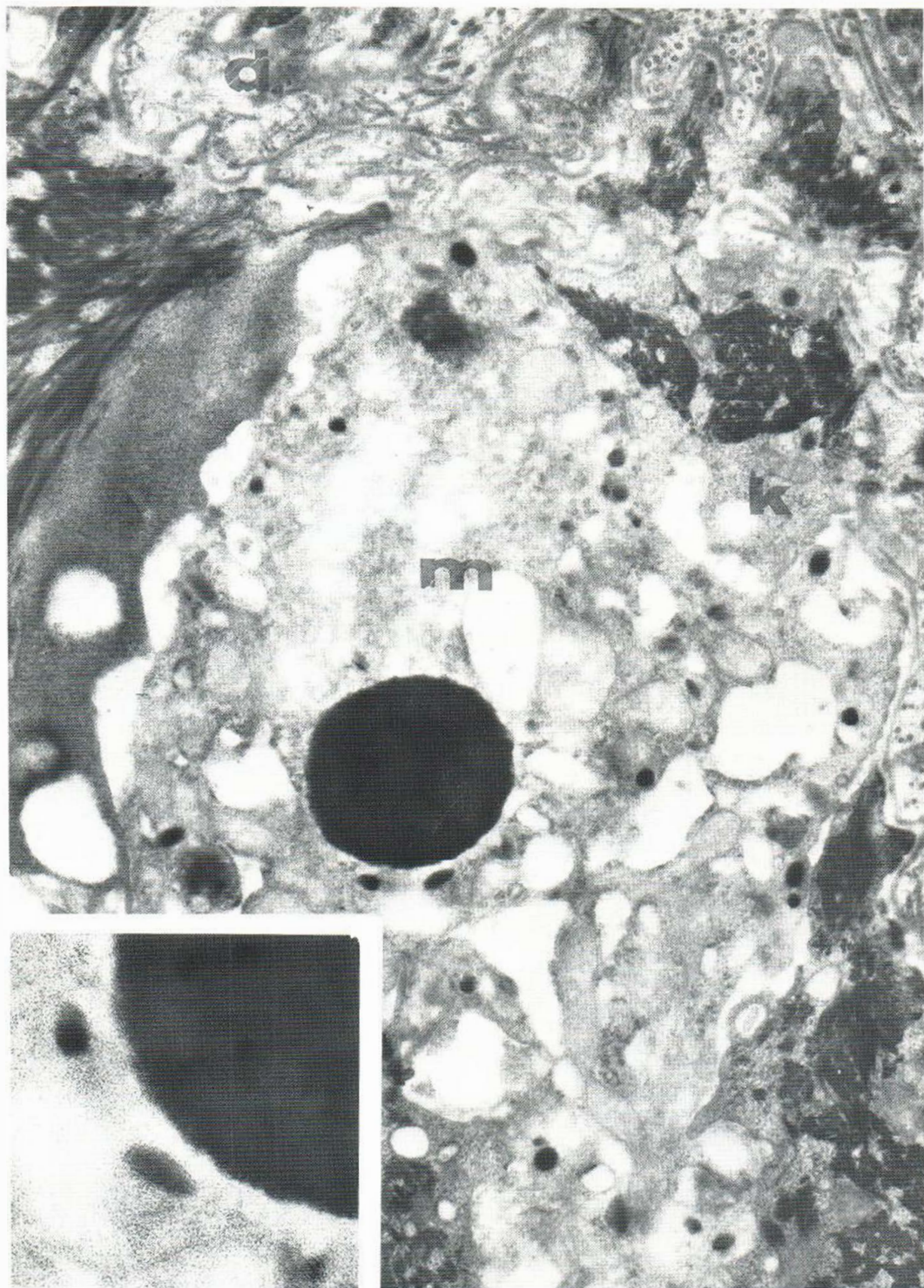


Fig. 2. Large granule of melanin in a melanocyte (*M*) whose endoplasmic reticulum is dilated and mitochondria swollen. *K*, keratinocyte; *D*, dermis ($\times 16\,300$). Inset:

Detail of a portion of the giant melanin granule. Compare with melanosome of normal size ($\times 40\,000$).

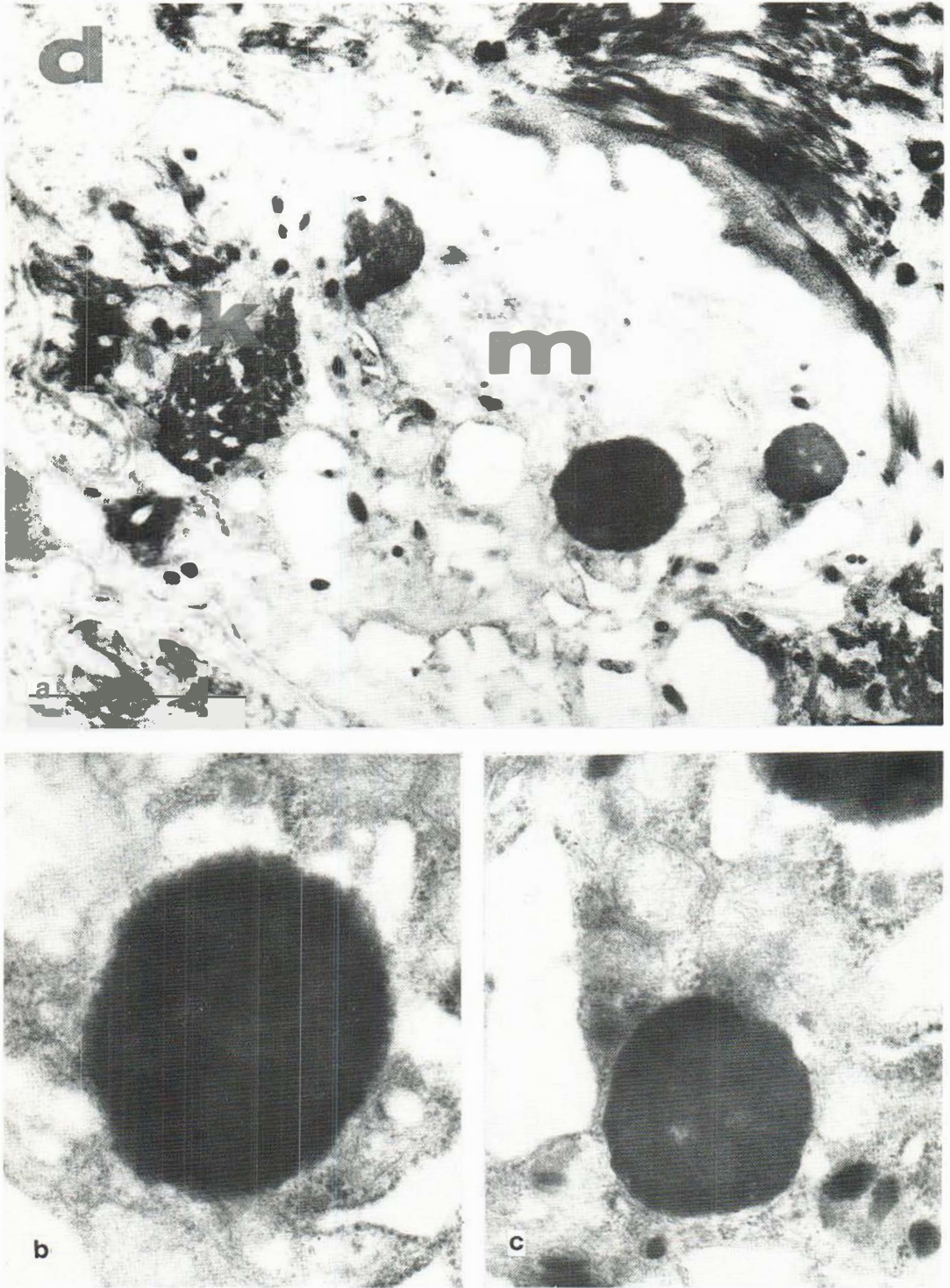


Fig. 3. a, melanocyte (M) containing 2 giant melanin granules. K, keratinocyte; D, dermis ($\times 13\,300$). b, detail of one of the giant granules of melanin ($\times 36\,600$). c, the structure of this grain is heterogeneous ($\times 37\,500$).

were dispersed throughout the cytoplasm. In addition to the giant pigment granules, mature melanosomes of normal size ($0.3 \times 0.1 \mu\text{m}$) were also present, particularly at the periphery of the cytoplasm.

In the zone between normal and depigmented skin, melanocytes not containing giant granules showed identical cytoplasmic alterations, occasionally with vacuoles with autophagocytosis of melanosomes.

Most of the melanocytes of healthy skin distant from the depigmented lesions were normal and contained melanosomes of normal size and form.

DISCUSSION

The giant pigment granules seen in certain melanocytes in the zone between normal and depigmented skin and in the adjacent normal skin appeared to consist of melanin.

They were obviously considerably larger than normal mature melanosomes. If by their size, these giant pigment granules can be compared to macromelanosomes described by Konrad et al. (10) and Jimbow et al. (6), their internal structure nevertheless tends to refute this. In fact, in none of these giant granules could we observe a complex internal structure with concentric zones corresponding to the various stages of melanization as described by the above authors. On the contrary, in our study the melanin grains had an homogeneous structure in which it was impossible to distinguish any basic elementary composition. Only one single granule seemed to be definitely heterogeneous but no internal structure could be discerned.

The granules which we observed were equally far removed from the classical description of macromelanosomes by the absence of peripheral membranes. The majority of authors—with few exceptions (2)—have always reported the presence of an external limiting membrane to the macromelanosomes.

It is difficult to reflect on the mechanism of formation of these structures in our case, particularly as, even in serial sections, we did not observe the intermediate stages of their formation. Giant particles of melanin can result from a derangement of morphogenesis at a distinct stage of melanosome ontogeny, as was suggested by Konrad et al. (10). It is possible also that these pigment masses correspond to the remains of melanophagosomes in

which the protein structure of the melanosomes had been destroyed. This degradation would take place in the melanocytes and would represent the final stage of an autophagocytic process of melanosomes. Our observation of numerous instances of melanosome autophagocytosis in the periphery of the achromic lesions would appear to support this concept.

The significance of macromelanosomes is unknown, since they are found in many and varied conditions, both genetic and non-familial and associated with both depigmentation and hyperpigmentation. It is important to note that our patient suffered from metastatic malignant melanoma. Konrad et al. (10) observed macromelanosomes in the skin of a patient with secondary diffuse melanosis resulting from malignant melanoma. The patient reported by Weiss & Zelickson (14) with the multiple lentiginosis syndrome, also suffered from a malignant melanoma.

ACKNOWLEDGEMENT

The technical assistance of Miss Agnès Micoud is gratefully acknowledged.

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Received February 20, 1978

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