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A second look at intraepithelial Langerhans cells in mycosis fungoides and related disorders

Ultrastructural study with special reference to Langerhans granules and virus-like particles*

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Summary. Skin biopsies of patients with small and large plaque parapsoriasis, premycotic lesions and mycosis fungoides in different stages were examined. Special attention was paid to the relationships between Langerhans cells (LC) and the neighbouring keratinocytes and lymphocytes. At the contact areas of LC and keratinocytes as well as LC and lymphocytes, particular cell membrane phenomena were observed. Aggregations of Langerhans granules and fusions of granules with LC plasma membranes were found exclusively at LC-keratinocyte interfaces. At LC-lymphocyte contact zones cell membrane appositions were seen.

In all cases investigated, virus-like particles were mainly found in LC and indeterminate cells (IDC). In 3 cases lymphocytes also contained these particles. It was of particular interest that virus-like particles were observed in skin specimens of all diseases investigated. Discrimination of these particles from other cellular organelles – especially lysosomes – was difficult, however.

The significance of our findings, particularly regarding to the supposed virus aetiology of cutaneous T cell lymphomas, is discussed.

Key words: Mycosis fungoides – Premycotic lesions – Parapsoriasis en plaques – Langerhans cells – Virus-like particles – Electron microscopy

Although mycosis fungoides (MF) is a rare disease with an incidence of 1–2 cases/million population/year (Burbank 1971; Clemmesen 1974; Greene et al. 1979; MacKie 1981) there is considerable interest in finding a convinc-

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ing concept for its aetiology and pathogenesis, which is, at least in the advanced stages, regarded as a cutaneous T-cell lymphoma (Thiers 1982). In most cases, MF develops from eczematous or psoriasiform lesions which have existed for months or years and which have not improved in spite of therapy. Large plaque parapsoriasis is the best known disease which may develop into MF in about 10% of cases (Samman 1976; Bonvalet et al. 1977). The other so-called premycotic diseases are ill defined and do not constitute nosologic entities (Samman 1979a; Haynes and Scott 1979). For this reason, the diagnosis of premycotic disease is a tentative one and can only be proven retrospectively.

In recent years environmental noxious and infectious agents have been discussed as aetiological factors for premycotic diseases and MF (Tan et al. 1974; Fischmann et al. 1979; Greene et al. 1979; Thiers 1982). A particular characteristic of MF represents the so-called Pautrier microabscesses, consisting of T-lymphocytes with cerebriform nuclei and of Langerhans cells (Burg and Braun-Falco 1977; Schmitt and Thivolet 1980; Souteyrand and Thivolet 1981; Jimbow et al. 1982). These T-lymphocytes are regarded as neoplastic T-cells. They were shown in most cases to possess helper cell functions (Berger et al. 1978) and to express the helper cell phenotype as demonstrated with hybridoma antibodies (Kung et al. 1981; Haynes et al. 1981 and 1982; Holden et al. 1982a and b; Tjernlund 1982).

Langerhans cells (LC) and their supposed precursor cells, indeterminate cells (IDC) (Rowden et al. 1979), are known to be of bone marrow origin (Katz et al. 1979; Tamaki et al. 1980) and to be related to the monocyte/macrophage system (Stingl et al. 1978a and 1980). They express certain histocompatibility antigens (Rowden et al. 1977; Stingl et al. 1978b; Rowden 1980) and are selectively recognized by particular monoclonal antibodies (Fithian et al. 1981; Murphy et al. 1981; Chu et al. 1982a; Dubertret et al. 1982; Löning et al. 1982). Functional studies on LC showed that they cooperate with T-lymphocytes and play a crucial role in antigen presentation and in allogeneic T-cell stimulation (Katz 1980). In addition, LC apparently act as initiators of hyperimmune responses in squamous epithelia (Silberberg et al. 1975; Silberberg-Sinakin and Thorbecke 1980). In MF, the initial event has been considered to be a stimulation of LC leading to disturbance of LC-lymphocyte interactions (Rowden et al. 1979). This particular stimulation of LC may be caused by exogenous environmental agents (Fischmann et al. 1979; Rowden and Lewis 1976).

Very recently, the hypothesis was presented by MacKie (1981) that initial viral infection of LC leads to LC dysfunction. This was postulated to be the cause of the characteristic helper cell aggregates in MF (MacKie 1981). The aforementioned hypothesis was supported by ultrastructural and virological investigations demonstrating intracellular C-type virus-like particles in skin lesions and lymph nodes of patients with MF and giving biochemical evidence of retroviruses in one of these cases (van der Loo et al. 1979). In addition, there are now several virological studies of T-cell lymphomas not only in Japan and the Caribbean, but also in North America and Europe

indicating retrovirus infection of lesional lymph nodes and peripheral blood cells (Poiesz et al. 1980a; Reitz et al. 1981; Poiesz et al. 1981; Kalyanaraman et al. 1981; Robert-Guroff et al. 1981; Miyoshi et al. 1981; Akagi et al. 1982; Gallo et al. 1982; Nakai et al. 1982; Yoshida et al. 1982). C-type retroviruses were described as particles with diameter ranging from 85 to 150 nm.

The present study on skin specimen of patients with parapsoriasis en plaques, so-called premycotic lesions and MF was done to elucidate the following questions:

1. Which are the ultrastructural characteristics of LC-lymphocyte and LC-keratinocyte interactions?
2. Are there particular observations with regard to the presence and distribution of Langerhans granules?
3. Can virus-like particles be identified and distinguished from other organelles of the same size?
4. Which are the cell types containing virus-like particles?

We looked for ultrastructural differences between parapsoriasis en plaques, so-called premycotic lesions and MF. To our knowledge comparative ultrastructural examination of the aforementioned questions has not yet been carried out.

Material and methods

1. Clinical data

The diagnosis of small plaque (case 1) and large plaque parapsoriasis (case 2) was made according to the criteria of Samman (1979b) and Lambert (1979). Up to 1983, no malignant transformation has been seen in case 2. Small plaque parapsoriasis never develops to cutaneous lymphomas (Bonvalet et al. 1977) (Table 1).

The tentative diagnosis of premycotic lesions (cases 3–5, stage 0 of CTCL staging) depended on the following findings: (1) Erythroderma or chronic eczematous or psoriasiform, pruritic dermatosis with large, slightly indurated and sometimes quite bizarre shaped plaques, (2) atypical response to therapy, and (3) the histopathologic findings of chronic or subacute eczema, of parapsoriasis en plaques, and eventually, of some irregular lymphocytes with hyperchromatic, atypical nuclei. Of these 3 cases, 2 (cases 4, 5) developed to MF later on. Case 3 was lost from observation.

The diagnosis of MF was established clinically and histologically (cases 6–10). Staging (Bunn and Lamberg 1979) was done retrospectively in most cases, according to the clinical findings. In each case, diagnosis was confirmed by follow-up examinations.

Prior to biopsy 6 patients had received different modalities of therapy (Tabe 1). In every case, therapy was stopped at least 4 days before biopsy was taken.

2. Tissues

Tissue was obtained from skin biopsies (Table 1). The specimens for electron microscopic study were cut into small pieces and immediately immersed in fixative (3% glutaraldehyde solution buffered with 0,1 M cacodylate, pH 7,2–7,4, postfixed with 2% osmium tetroxide in 0,1 M cacodylate buffer). After dehydration in a graded alcohol series, embedding was done in Epon 812. Thin and ultrathin sections were cut on a Reichert – Jung OmU 3. The ultrathin sections were contrasted with alcoholic uranyl acetate and lead citrate. Ultrastructural examinations were done by two authors independently with a Zeiss EM 9 S-2 electron microscope.

Table 1.

Patient data						
No	Journal No	Sex	Age	Diagnosis	Stage	Prior treatment
1	103/81	m	63	Parapsoriasis en petits plaques	∅	Topical corticosteroids
2	137/81 138/81	f	68	Parapsoriasis en grands plaques	∅	Topical corticosteroids
3	10/79	m	59	Premycotic lesions	∅	∅
4	135/81	f	51	Premycotic lesions[a]	0[b]	∅
5	43/79	m	56	Erythrodermia (premycotic)[a]	0[b]	Topical corticosteroids
6	181/82	m	81	Mycosis fungoides (MF)	I B	∅
7a	16/79	f	22	MF	I B	∅
7b	119/81	f	25	MF	II A	Teleroentgen therapy
8	641/78	m	46	MF	IV A	Teleroentgen therapy, PUVA
9	3/79	m	74	MF	IV B	?[c]
10	129/81	f	74	MF	IV B	Topical corticosteroids

[a] Premycotic lesions which progressed to MF later on
[b] Stage 0 = premycotic lesions which progressed to MF later on
[c] Data not available

Results

Except for the occurrence of Pautrier microabscesses in 3 cases of mycosis fungoides (MF) – cases 7a, 7b, 8 – the cases of parapsoriasis en plaques, premycotic lesions and MF did not reveal significant ultrastructural differences which regard to the following details:

Relationships between Langerhans cells (LC), lymphocytes and keratinocytes

Two principal non-epithelial cellular elements were found: LC and their supposed precursor cells (indeterminate cells = IDC), and lymphocytes. LC contained large nuclei with marginally located heterochromatin and showed an organelle rich elongated cytoplasm including typical Langerhans granules (Fig. 1a). A large number of typical LC were seen in the cases with small and large plaque parapsoriasis (case 1, 2), in one premycotic lesion (case 4) which progressed to MF later on and in one case with MF (case 7), which progressed over 3 years from stage I B to II A. LC were frequently found to be in close contact with lymphocytes containing indented electron dense nuclei rich in heterochromatin. Those lymphocytes contained rather

Ultrastructural results						
LC[d]	IDC	LY	Keratinocyte degeneration	Virus-like particles in[f]		
				LC	IDC	LY
+++	++	++	not evident (n.e.)	+++	+++	∅
+++	++	++	evident (e.)	+++	+++	+
+	+++	++	e.	+++	+++	+
++	++	++	n.e.	+++	+++	∅
∅	++	++	n.e.	∅	++	∅
+	++	+++	e.	+++	++	∅
++	++	+++	e.	+++	+	+
+++	++	+	e.	+++	∅	∅
++	++	++	e.[e]	∅	++	∅
∅	++	+++	e.	∅	++	∅
∅	++	++	n.e.	∅	++	∅

[d] + = less than 10% of all documented cells; ++ = 10 to 40% of all documented cells; +++ = more than 40% of all documented cells

[e] In addition, in this case lymphocyte degeneration was striking

[f] + = less than 10% of the respective documented cell type; ++ = 10 to 40% of the respective documented cell type; +++ = more than 40% of the respective documented cell type

few cytoplasmic organelles (Fig. 1a, b). In all investigated cases more than 10% of the documented cells were lymphocytes (Table 1). In 3 cases of MF lymphocytes and LC formed typical Pautrier microabscesses (Fig. 1a). Appositions of the outer cell membranes of LC and lymphocytes were occasionally seen (inset Fig. 1a). One case of MF (case 8) showed marked lymphocyte degeneration (Fig. 1b). Degeneration of lymphocytes was indicated by severe vacuolization of the cytoplasm.

Keratinocytes in the vicinity of lymphocytes showed occasionally severe degenerative changes. They lost their filamentous structure and their cytoplasmic organelles and developed large vacuoles (Fig. 1b).

Langerhans granules

LC-keratinocyte contacts were frequently associated with the occurrence of a large number of Langerhans granules in these zones (Fig. 2a). At these contacts, a very interesting observation was the relationship of granules to the LC-membranes, i.e. Langerhans granules were found to be fused

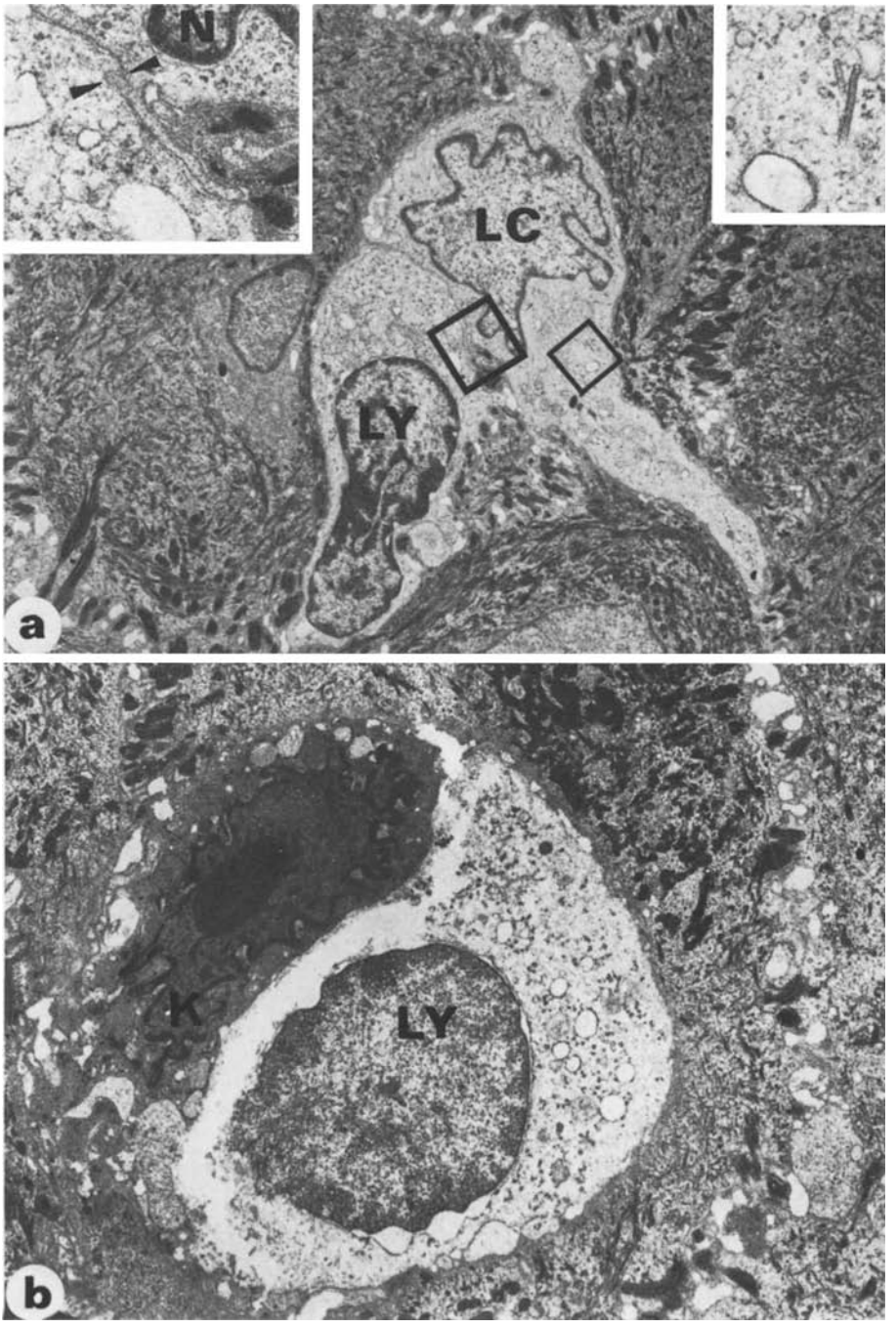

Fig. 1 a, b. (**a**) Pautrier microabscesses showing the close relationship of a Langerhans cell (*LC*) and a lymphocyte (*LY*). Magnification ×4,500. *Inset, left side*: Contact area of outer cell membranes, which appear to be apposed in a circumscribed zone. Magnification ×24,000. *Inset, right side*: Higher magnification of LC granules. Magnification ×30,000. (**b**) Relationship of keratinocyte (*K*) and lymphocyte (*LY*). Degeneration of keratinocyte showing condensed nuclear chromatin, dissoluted cytoplasmic architecture and loss of cellular junctions. Intercellular space between keratinocyte and lymphocyte may be a consequence of shrinking due to impaired intercellular cohesion. Magnification ×8,500

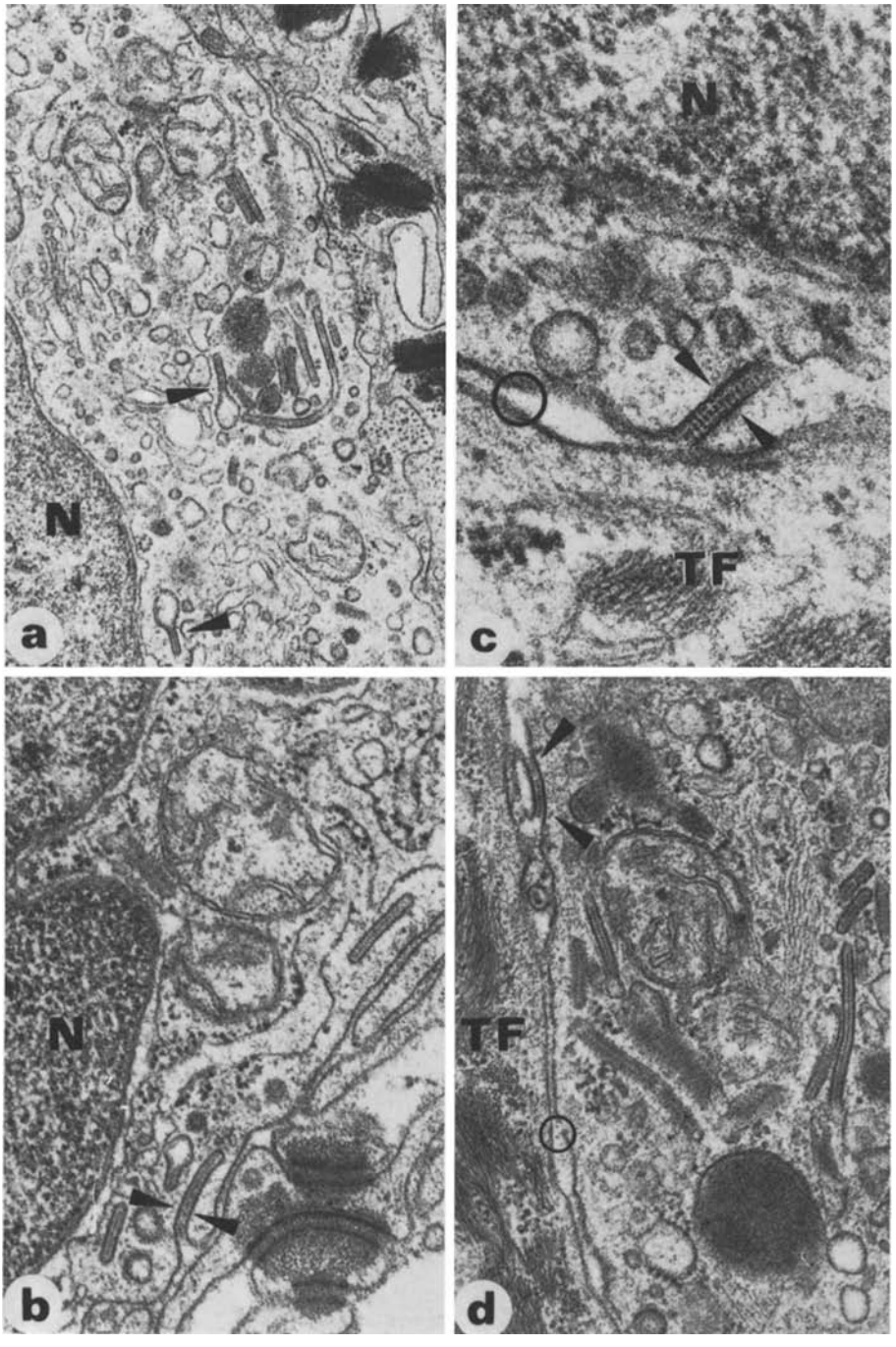

Fig. 2a–d. (**a**) Typical rod-shaped and racket-shaped Langerhans granules (*arrowheads*) in close vicinity to desmosomes. *N* = nucleus. Magnification × 27,000. (**b, c**) Relationships of the granules to the LC-membranes at the LC-keratinocyte interfaces (*black circle*). Arrowheads point to LC granules fused with outer cell membranes. *N* = nucleus, *TF* = tonofibrils. Magnification **b** × 41,000, **c** × 85,000. (**d**) LC granule appears to be located outside the cell-body (*arrowheads*). *TF* = tonofibrils. Magnification × 41,000

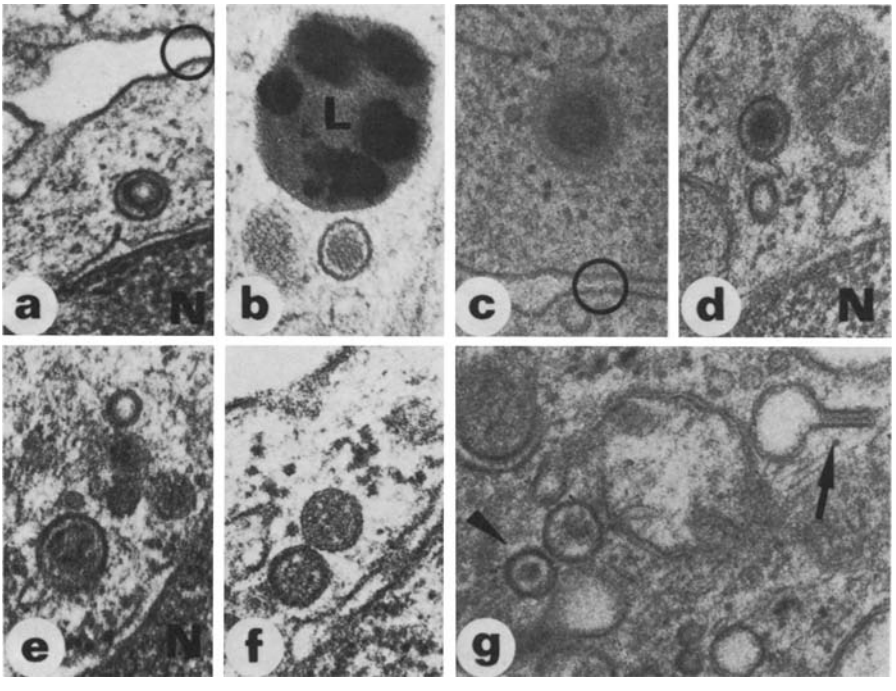

Fig. 3a–g. Virus-like particles in indeterminate cells and lymphocytes. **(a–d)** *L* = lysosome, *N* = nucleus. Magnification **a**, **b**, **d** × 58,000, **c** × 65,000. **(e–g)** Virus-like particles in Langerhans cells with granules (*arrow*) in cytoplasm. *N* = nucleus. Magnification **e–g** × 58,000

with the outer membranes of LC (Fig. 2b–d). This phenomenon was not observed at the LC-lymphocyte interfaces. Langerhans granules showed the characteristic internal structures with median striated lines. These cytoplasmic granules appeared as rod-shaped, flash-shaped or tennis-racket-shaped and as circular particles. It was notable that a large number of LC with typical granules were found in patients with small and large plaques parapsoriasis (Table 1).

Virus-like particles

Apart from Langerhans granules, the cytoplasm of LC contained a large number of mitochondria, lysosomes and vesicles of various size. We designated dense bodies with a diameter of 85 to 150 nm, with a variably electron dense core, and with a surrounding unit membrane (Fig. 3) as virus-like particles. All ultrastructural pictures of LC, so-called indeterminate cells (cells with all other characteristics of LC except Langerhans granules), lymphocytes, melanocytes and keratinocytes (in total 400 photographs of different cells) were evaluated for the presence of these virus-like particles. We should emphasize that we found such particles (Fig. 3) in *all* investigated cases. About 40% of photographically documented intraepidermal LC and

about 35% of intraepidermal indeterminate cells (IDC) contained virus-like particles. In 3 cases (case 2: parapsoriasis en grands plaques, case 3: premycotic lesion, case 7a: MF stage I B) virus-like particles were observed in cells with the ultrastructural aspects of lymphocytes. Only 4% of lymphoid cells were seen to possess virus-like particles. Although defined by their diameter and structure, virus-like particles were often hard to distinguish from cytoplasmic vesicles and primary lysosomes. However, such particles were unequivocally found neither in keratinocytes nor in melanocytes.

Discussion

In this morphological study non-epithelial cells (Langerhans cells (LC), indeterminate cells (IDC) and lymphocytes) in specimens from patients with small and large plaque parapsoriasis, with premycotic lesions, and with different stages of mycosis fungoides (MF) were investigated ultrastructurally with special regard to the presence and intracellular distribution of Langerhans granules and to the occurrence of virus-like particles. Although interpreting our semiquantitative data with caution, it was striking that high proportions of LC with typical granules were found in patients with small and large plaque parapsoriasis. Apart from LC there were a large number of IDC in all cases. These cells represent non-epithelial cells with morphological and immunological characteristics of LC, but do not contain Langerhans granules (Rowden et al. 1979; Thorbecke et al. 1980). It is the present belief that IDC are precursor cells of LC (Rowden et al. 1979). Immunological studies using hybridoma antibodies have shown that LC and their supposed precursors may be increased in cutaneous T-cell lymphomas and their prestages (MacKie and Turbitt 1982; Chu et al. 1982b; Holden et al. 1982a; Meissner et al. 1983).

Marked epidermotropism of lymphocytes were found in small and large plaque parapsoriasis, in premycotic lesions, and in confirmed MF. Typical Pautrier microabscesses were seen in 3 cases of MF. These peculiar cell aggregates are formed by lymphocytes and LC (Burg and Braun-Falco 1977; Schmitt and Thivolet 1980; Souteyrand and Thivolet 1981; Jimbow et al. 1982), intermingled and surrounded by degenerating keratinocytes.

It was an interesting and conspicious finding that Langerhans granules were particularly concentrated at LC-keratinocyte interfaces. In those areas Langerhans granules were occasionally fused with plasma cell membranes. Parts of Langerhans granules appeared to be located outside the LC-body. At present, it cannot be decided whether this phenomenon is part of exocytotic or endocytotic mechanisms (El-Labban 1982). The observation of these fusions taking exclusively place at LC-keratinocyte connections point to a role of Langerhans granules in LC-keratinocyte interactions. In vitro investigations showed that epidermal cells can induce lymphoid cell differentiation (Patterson and Edelson 1982). These functions of keratinocytes may be relevant for LC differentiation, too. In this context, it is interesting that both thymus epithelial cells and keratinocytes of skin produce thymic hormone-like substances (FTS = facteur thymique serique) influencing differen-

tiation of T-lymphocytes (Kato et al. 1981) and that both thymocytes and LC carry similar differentiation components at their cell membranes recognized by OKT 6 monoclonal antibodies (Fithian et al. 1981; Haynes 1981). At LC-lymphocyte interfaces, cell membranes were closely apposed. At these sites Langerhans granules were not seen. Interactions of LC and lymphocytes are thought to take place via the production of interleukin II (Gazdar et al. 1979; Poiesz et al. 1980b).

In some cases (1 case with erythroderma as a premycotic eruption and 2 of 3 cases with advanced stages of MF) we did not find LC with typical granules. This observation may be explained in two ways. First, it is well known that the detection of Langerhans granules increases with the number of ultrathin sections examined (Rowden et al. 1979; Thorbecke et al. 1980). This technical problem plays a role in every ultrastructural study on LC and IDC. Secondly, the aggregation of histiocytoid cells lacking typical Langerhans granules was described in advanced stages of MF (Schmitt and Thivolet 1980).

In our study it was evident that heterogenity of intraepithelial non-epidermal cell populations was a feature of all investigated cases. Indeed, recent data on cutaneous T-cell lymphoma examined with monoclonal antibodies showed that the cutaneous infiltrates consisted not only of helper T-lymphocytes, but contained also other T-cell phenotypes and LC (Kung et al. 1981; Haynes et al. 1981 and 1982; Holden et al. 1982a).

A relationship between chronic inflammatory processes of skin and neoplasia was discussed by Tan et al. (1974) and Thiers (1982): Persistent antigenic stimulation by exogenous allergens may lead to a breakdown of the local immune homiostasis and, eventually, to an overt malignancy. Nowadays, older views on the aetiology of skin neoplasias have been enlarged by synergistic concepts, taking into account the effects of exogenous agents (Greene et al. 1979; Cohen et al. 1980) and of viruses as initiating factors (zur Hausen 1980; MacKie 1981). Oncogenic DNA- and RNA-viruses are known to be concerned in experimental and human premalignant and malignant lesions of different histogenesis (zur Hausen 1977, 1980, and 1982; Reid et al. 1982; Odajima and Solt 1982; Gissmann et al. 1983).

For mycosis fungoides, the hypothesis was presented that an initial viral infection of the immune competent epidermal Langerhans cell may lead to faulty LC-lymphocyte interactions which subsequently cause persistent chronic infection (MacKie 1981). At present, this hypothesis is supported by several findings: In skin biopsies from patients with MF and Sézary syndrome and in some lymph nodes from patients with MF C-type virus-like particles were found in the cytoplasm of LC and IDC at the ultrastructural level. In one case, these findings were confirmed by biochemical studies demonstrating RNA-dependent DNA polymerase activity (van der Loo et al. 1979). In T-cell lymphoblastoid cell lines derived from patients with cutaneous T-cell lymphomas and leukemias (CTCL) (Poiesz et al. 1980a and 1981; Kalyanaraman et al. 1981; Reitz et al. 1981; Robert-Guroff et al. 1981; Gallo et al. 1982) and from patients with adult T-cell leukemia (ATL) (Hinuma et al. 1981; Miyoshi et al. 1981; Akagi et al. 1982; Nakai et al.

1982; Yoshida et al. 1982) virus-like particles with the biochemical, immunological and morphological characteristics of type C retroviruses (particle size ranging from 85 to 150 nm in the various studies) were detected.

In all cases investigated we found particles of the stated diameter, containing centrally located nucleoids and surrounded by a viral envelope. In agreement with the study of van der Loo et al. (1979) on MF cases, we found virus-like particles predominantly in LC and IDC. In 3 of our cases (1 case with large plaque parapsoriasis, 1 case with the tentative diagnosis of premycotic eruption and 1 case with MF stage I B) lymphocytes also contained virus-like particles. However, in contrast, those particles were not seen in melanocytes and keratinocytes in any case investigated.

LC seem to be the target cells in other viral infections, as in MF (Nagao et al. 1976).

Although our knowledge on the size and structure of retroviruses has been greatly improved by cell culture studies (Poiesz et al. 1980a and 1981; Hinuma et al. 1981; Kalyanaraman et al. 1981; Miyoshi et al. 1981; Reitz et al. 1981; Robert-Guroff et al. 1981; Akagi et al. 1982; Gallo et al. 1982; Nakai et al. 1982; Yoshida et al. 1982) misinterpretations are likely to occur due to the presence of other cell organelles similar in diameter and structure (e.g. vesicles, primary lysosomes). Electron microscope studies, and even more sophisticated methods (in situ hybridization technique), will not be able to determine whether viruses are merely passengers in Langerhans cells. At present, we can only state that particles with the characteristics of retroviruses are exclusively found in LC, IDC and in some lymphocytes, not only in mycosis fungoides but also in small and large plaque parapsoriasis and in premycotic lesions.

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