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Immunohistochemical study of epidermal Langerhans cells and dermal dendritic cells in benign and malignant skin lesions characterized by a dermal lymphoid infiltrate consisting either of B-cells or T-cells*

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Summary. Skin biopsies from 43 patients with a rather dense dermal lymphoid infiltrate of either inflammatory or neoplastic nature have been investigated. We studied the number, distribution and immunophenotype of epidermal Langerhans cells and dermal dendritic cells. As previously reported, differences in epidermal Langerhans cell and dermal dendritic cell numbers between skin biopsies with a B-cell infiltrate and skin biopsies with a T-cell infiltrate were found, dendritic cells being more numerous in the latter. The main finding of this study was an uneven distribution of epidermal Langerhans cells and dermal dendritic cells in skin biopsies with a T-cell infiltrate: in skin lesions with an inflammatory lymphoid infiltrate, small clusters of epidermal and dermal dendritic cells admixed with T-lymphocytes (predominantly T-helper/inducer cells) and small blood vessels were present at areas of exocytosis. In skin lesions with a neoplastic lymphoid infiltrate larger, more loosely arranged aggregates of dendritic cells and T-cells were seen. These cell aggregations composed of activated (inflammatory or neoplastic) T-cells and dendritic cells may represent the cutaneous homologue of the secondary T-nodule in the lymph node. Both types of cell aggregates may correspond to the dendritic cell-T cell clusters observed in in vitro induced immune responses.

Key words: Immunohistochemistry – Langerhans cells – Antigen presenting cells – Skin disorders

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Introduction

The skin may be affected by B-cell lymphomas, T-cell lymphomas or lesions presenting with a rather dense dermal inflammatory lymphoid infiltrate. The composition of the dermal infiltrate in all three situations has been well characterized by immunohistochemistry. B-cell lymphomas, a heterogeneous group of non Hodgkin lymphomas, are composed of cells displaying one or more B-cell characteristics (McDonald 1982). Most cutaneous T-cell lymphomas are composed of helper/inducer T-cells (Buechner et al. 1983, 1984; Chu et al. 1984; Cox et al. 1986; Haynes et al. 1981, 1982; Holden et al. 1982; Kung et al. 1981; Lacour et al. 1986; McMillan et al. 1982b; Nasu et al. 1985; Piepkorn et al. 1984; Ralfkiaer et al. 1985a; Schmitt et al. 1982; Sudo and Morohashi 1986; Thomas et al. 1982; Tosca et al. 1986; Willemze et al. 1983). Only a few cases consisting of cytotoxic/suppressor T-cells have been described (Buechner et al. 1984; Chu et al. 1984; Cox et al. 1986; Haynes et al. 1982; Meissner et al. 1983; Nasu et al. 1985; Ohkochchi et al. 1986; Piepkorn et al. 1984; Ralfkiaer et al. 1985a). Most skin lesions with a dermal inflammatory infiltrate are composed of T-cells with a predominance of helper/inducer T-cells (Buechner et al. 1984; McMillan et al. 1982c, 1982d, 1985; Ralfkiaer et al. 1985b; Willemze et al. 1984a, b) In lymphocytoma cutis, the dermal infiltrate is largely composed of B-cells (Geerts and Kaiserling 1985; Ralfkiaer et al. 1984; Van Hale and Winkelmann 1985).

In contrast with the numerous data available on the morphology and immunophenotype of the lymphoid cells in these skin lesions, the alterations of Langerhans cells and dermal dendritic cells have been less extensively studied. Therefore, we analyzed the distribution and immunophenotype of

Table 1. Skin lesions with dermal B-cell imfiltrate

Case	Diagnosis	Immunophenotpye of dermal infiltrate	LC	DDC
1–5	lymphocytoma cutis	HLA-DR$^+$, $BA_1{}^+$, $B_1{}^+$, positivity for κ and λ	++	±
6	NHL diffuse, mixed cell	HLA-DR$^+$, $BA_1{}^-$, $B_1{}^+$, no demonstrable heavy chains, κ^+	++	±
7	NHL immunoblastic	HLA-DR$^+$, $BA_1{}^+$, $B_1{}^+$, no demonstrable heavy chains, κ^+	+	±
8	NHL immunoblastic	HLA-DR$^+$, $BA_1{}^+$, $B_1{}^-$, μ^+, λ^+	+	±
9	NHL immunoblastic	HLA-DR$^-$, $BA_1{}^-$, $B_1{}^-$, μ^+, κ^+	++	±
10	NHL diffuse, large cell	HLA-DR$^+$, $BA_1{}^+$, $B_1{}^+$, μ^+, κ^+	+	±
11	NHL diffuse, large cell	HLA-DR$^+$, $BA_1{}^-$, $B_1{}^+$, μ^+, κ^+	++	±
12–19	NHL diffuse, large cell	HLA-DR$^+$, $BA_1{}^+$, $B_1{}^+$, no demonstrable heavy chains, κ^+	+	+

NHL: non Hodgkin lymphoma; LC: Langerhans cell; DDC: dermal dendritic cell; ± → + +: estimate of the number of cells stained

Table 2. Skin lesions with dermal T-cell infiltrate

Case	Diagnosis	Immunophenotype of dermal infiltrate	LC	LC Clusters	DDC	DDC at DEJ
14	Jessner infiltrate	HLA-DR$^+$, Leu-1$^+$, $OKT_4{}^+ \simeq OKT_8{}^+$	++	+	++	+
15 → 17	Jessner infiltrate	HLA-DR$^+$, Leu-1$^+$, $OKT_4{}^+ \simeq OKT_8{}^+$	++	−	+	−
18	lymphomatoid contact dermatitis	HLA-DR$^+$, Leu-1$^+$, $OKT_4{}^+ \simeq OKT_8{}^+$	++	+	+++	−
19–20	parapsoriasis en plaques (SF)	HLA-DR$^+$, Leu-1$^+$, $OKT_4{}^+ > OKT_8{}^+$	++; +++	+	+	+
21 → 24	parapsoriasis en plaques (SF)	HLA-DR$^+$, Leu-1$^+$, $OKT_4{}^+ > OKT_8{}^+$	+++	+	++	−
25–26	parapsoriasis en plaques (SF)	HLA-DR$^+$, Leu-1$^+$, $OKT_4{}^+ \gg OKT_8{}^+$	++++	+	+; +++	+
27	parapsoriasis en plaques (SF)	HLA-DR$^+$, Leu-1$^+$, $OKT_4{}^+ \simeq OKT_8{}^+$	+++	+	++	+
28	parapsoriasis en plaques (SF)	HLA-DR$^+$, Leu-1$^+$, $OKT_4{}^+ > OKT_8{}^+$	+++	+	++	+
29	parapsoriasis en plaques (SF)	HLA-DR$^+$, Leu-1$^+$, $OKT_4{}^+ > OKT_8{}^+$	++	+	+	−
30	parapsoriasis en plaques (SF)	HLA-DR$^+$, Leu-1$^+$, $OKT_4{}^+ > OKT_8{}^+$	+++	−	++	−
31	parapsoriasis en plaques (LF)	HLA-DR$^+$, Leu-1$^+$, $OKT_4{}^+ \gg OKT_8{}^+$	+++	+	+	−
32–33	parapsoriasis en plaques (LF)	HLA-DR$^+$, Leu-1$^+$, $OKT_4{}^+ > OKT+$	+++	+	++	+
34	MF	HLA-DR$^+$, Leu-1$^+$, $OKT_4{}^+ \gg OKT_8{}^+$	+++	+	++	+
35–36	MF	HLA-DR$^+$, Leu-1$^+$, $OKT_4{}^+ \gg OKT_8{}^+$	+++	+	+++	−
37	MF	HLA-DR$^+$, Leu-1$^+$, $OKTO_4{}^+ \gg OKT_8{}^+$	+++	+	+++	+
38–39	MF	HLA-DR$^+$, Leu-1$^{-/+}$, $OKT_4{}^+ > OKT_8{}^+$	+++	+	+++	+
40	MF	HLA-DR$^+$, Leu-1$^+$, $OKT_4{}^+ \gg OKT_8{}^+$	+++	−	++	−
41	MF	HLA-DR$^+$, Leu-1$^-$, $OKT_4{}^- > OKT_8{}^+$	++	−	+	+
42	MF	HLA-DR$^+$, Leu-1$^+$, $OKT_4{}^+ \gg OKT_8{}^+$	++	+	++	+
43	MF	HLA-DR$^+$, Leu-1$^+$, $OKT_8{}^+ \gg OKT_4{}^+$	++	−	+++	−
44	MF	HLA-DR$^+$, Leu-1$^-$, $OKT_8{}^+ \gg OKT_4{}^+$	+++	−	+	+
45	SS	HLA-DR$^+$, Leu-1$^-$, $OKT_4{}^+ \gg OKTO_8{}^+$	++	+	+	−

SF: small plaque form; LF: large plaque form; MF: mycosis fungoides; SS: Sézary syndrome; LC: Langerhans cells; DDC: dermal dendritic cell; DEJ: dermo-epidermal junction; + → + + + +: estimate of the number of cells stained

dendritic cells in skin biopsies with B-cell lymphomas, T-cell lymphomas and benign "pseudolymphomatous" conditions.

Materials and methods

Skin biopsies from 43 patients taken for diagnostic purposes were available for this study.

Part of each biopsy was fixed in Bouin's solution and processed for conventional light microscopy. A representative part of each biopsy was quickly frozen in liquid nitrogen-cooled isopentane and stored at −80° C until used for immunohistochemistry.

All lesions were diagnosed on paraffin embedded, H & E stained sections according to the criteria of Lever (Lever and Schaumburg-Lever 1983) and morphological diagnoses were correlated with clinical data. All cases are listed in Tables 1 and 2. For the demonstration of cell surface antigens an indirect immunoperoxidase procedure was performed (Graham et al. 1965; Mason et al. 1982). The following monoclonal antibodies were applied on semiserial frozen sections: anti-HLA-DR (common framework of the HLA-DR or Ia-like antigen), OKT_6 (cortical thymocytes, Langerhans cells), Leu-1 (pan T-cell marker), OKT_4 (T-helper/inducer cells), OKT_8 (T-cytotoxic/suppressor cells), BA_1 (B-lymphocytes, granulocytes), B_1 (B-lymphocytes), TO_5 (C_{3b} receptor) and antisera against heavy chains mu, gamma and delta and light chains kappa and lambda. Anti-HLA-DR, Leu-1 and antisera against kappa and lambda were purchased from Becton-Dickinson, Sunnyvale, Ca; OKT_4, OKT_8 and OKT_6 from Ortho Pharmaceuticals Co, Raritan, NJ; BA_1 from Hybritech, La Jolla, Ca; B_1 from Coulter Electronics, Hialeah, Florida; TO_5 and antisera against mu, gamma and delta from Dakopatts a/s, Copenhagen, Den-

mark. A polyclonal anti-S_{100} antiserum (S_{100} being a Ca^{2+}-binding protein present in different cell types a.o. in dendritic cells) (Dakopatts a/s, Copenhagen, Denmark) was applied on paraffin sections.

Cell numbers were estimated semiquantitatively.

An alkaline phosphatase staining, modified after the method of Gomori (Barka and Anderson 1965), was performed at pH 9.2 using Na-β-glycerophosphate as substrate and using a range of incubation times.

Results

According to the composition of the dermal infiltrate, we have divided our cases in 2 groups. Group 1 contains skin lesions in which the dermal infiltrate is largely composed of inflammatory or tumour B-cells. Group 2 consists of benign and malignant skin lesions in which the dermal infiltrate is almost entirely composed of inflammatory or tumour T-cells.

In skin lesions with dermal B-cell infiltrate (cases 1–11) (see Table 1) a dense dermal (and hypodermal) lymphoid infiltrate with a free border zone was present in all cases, showing either a nodular pattern (cases 1–3, 5, 7, 8) or a diffuse distribution (cases 4, 6, 9–13).

This infiltrate consisted mainly of HLA-DR^+ lymphoid cells, expressing one or more B-cell markers. $TO_5{}^+$ dendritic reticulum cells were present within the B-cell aggregates in cases 1 and 3. At the borders of this B-cell infiltrate and in the perivascular areas, a variable amount of mature T-lymphocytes was recognized.

The number of epidermal Langerhans cells was within the normal range. They were mainly localized in the basal part of the epidermis (Fig. 1). $OKT_6{}^+$ Langerhans cells outnumbered $S_{100}{}^+$ and HLA-DR^+ Langerhans cells.

Few HLA-DR^+ and $S_{100}{}^+$ dermal dendritic cells were found; $OKT_6{}^+$ dermal dendritic cells were almost absent (Fig. 1). If present, these cells occurred predominantly in the border zone or within agggregates of mature T-lymphocytes.

No HLA-DR expression on keratinocytes was seen, except for cases 5, 8 and 13. $OKT_6{}^+$ keratinocytes were present in cases 1, 6, 9, 11 and 13.

In skin lesions with dermal T-cell infiltrate (cases 12–43) (see Table 2) the dermal infiltrate showed a perivascular (and periadnexal) distribution in cases 14–30. Spongiosis and/or exocytosis was noted in cases 18–30. In cases 31–45 a more or less dense band-like infiltrate was present in the upper dermis. In these cases a variable degree of epidermotropism was seen, the latter being extremely pronounced in cases 43 and 44.

In all cases, the dermal lymphoid infiltrate was mainly composed of HLA-DR^+, $OKT_4{}^+$ T-cells, except for cases 42 and 43 in which HLA-DR^+, $OKT_8{}^+$ T-cells predominated. Expression of the Leu-1 antigen was completely lost in cases 38, 41, 44 and 45.

A rather large number of epidermal Langerhans cells and dermal dendritic cells was noted. $OKT_6{}^+$ Langerhans cells were more numerous and showed better developed dendritic processes than HLA-DR^+ and/or $S_{100}{}^+$ Langerhans cells. HLA-DR^+ dermal dendritic cells outnumbered $OKT_6{}^+$ and $S_{100}{}^+$ dermal dendritic cells. These cells were dispersed throughout the lymphoid infiltrate.

In 24 out of 32 cases a strikingly uneven distribution of HLA-DR^+, $S_{100}{}^+$ and/or $OKT_6{}^+$ dendritic cells was seen. Small clusters composed of epidermal Langerhans cells, dermal dendritic cells and T-lymphocytes, predominantly T-helper/inducer cells occurred at areas of exocytosis in cases 14, 18–29, 31 and 32 (Fig. 2). Within these clusters few small alkaline phosphatase positive blood vessels were present. Larger, more loosely arranged collections of dendritic cells (epidermal Langerhans cells and dermal dendritic cells) and tumour T-cells were found in cases 33–39, 42 and 45 (Fig. 3).

A discontinuous monolayer of HLA-DR^+ dermal dendritic cells was seen at the dermo-epidermal junction in 16 cases. In cases 28 and 37 some of these cells expressed the T_6-antigen.

HLA-DR expression on the keratinocytes was seen in cases 24, 26, 27, 29, 31, 32, 35, 39–42, 44 and 45. $OKT_6{}^+$ keratinocytes were recognized in cases 26–28, 30, 32–35, 39 and 44.

Discussion

We have studied the distribution and immunophenotype of Langerhans cells and dermal dendritic cells in skin lesions characterized by the presence of a more or less dense dermal lymphoid infiltrate either composed of B-cells or of T-cells. As previously reported (Drijkoningen et al. 1986; Muhlbauer et al. 1982; Thomas et al. 1982) $OKT_6{}^+$ Langerhans cells outnumberd HLA-DR^+ Langerhans cells in all cases, while HLA-DR^+ dermal dendritc cells were more numerous than $OKT_6{}^+$ dermal dendritic cells. OKT_6 and anti-HLA-DR visualize phenotypically different Langerhans cell subsets, present at different epidermal levels. They probably represent functionally different conditions of the same cell (Drijkoningen et al. 1986).

In skin lesions with a B-cell infiltrate normal numbers of epidermal Langerhans cells are present

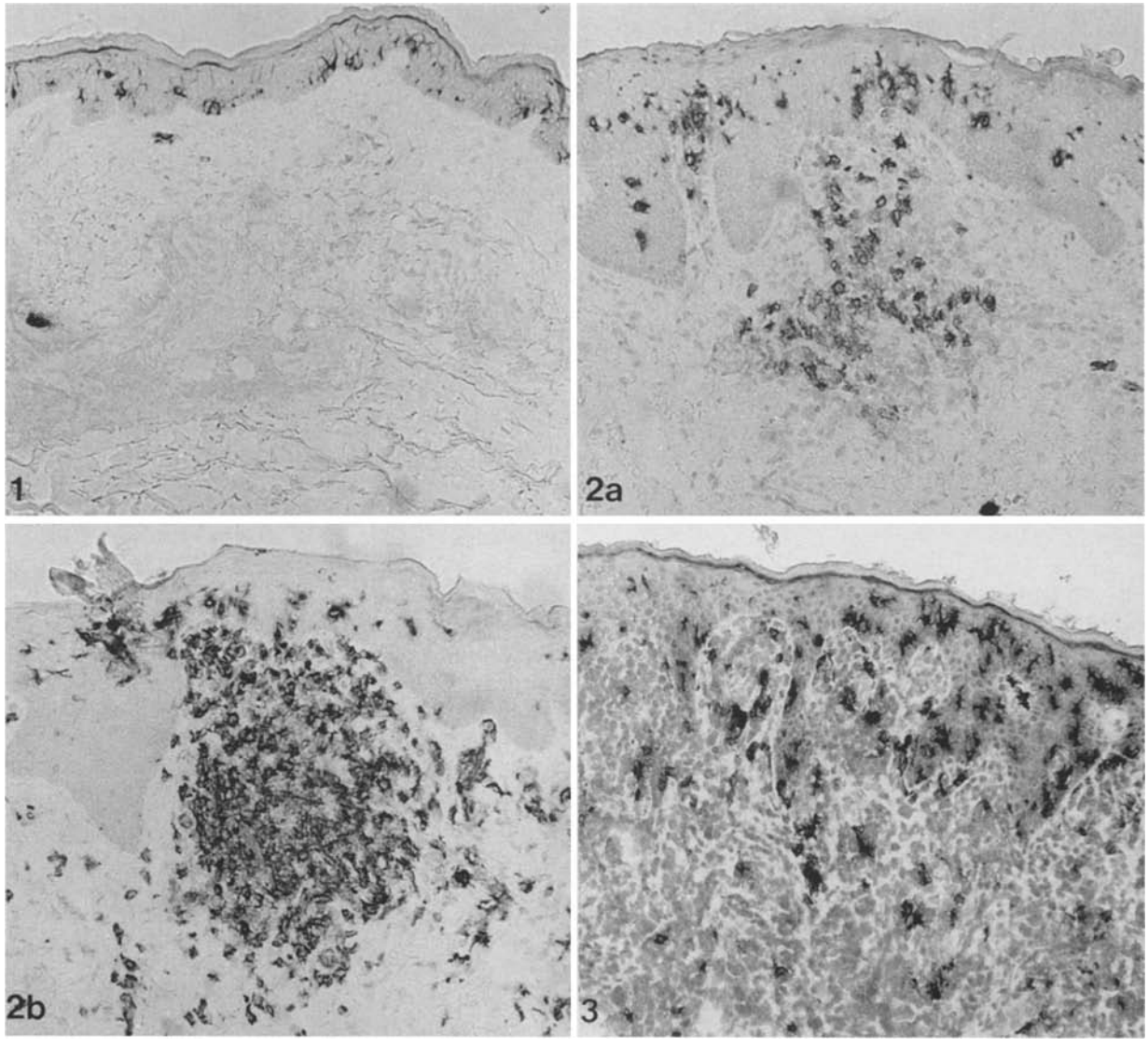

Fig. 1. Frozen section of case 9 (NHL diffuse, large cell) stained with OKT_6. The number of OKT_6^+ Langerhans cells is not elevated and they are mainly localized in the basal part of the epidermis. Only one OKT_6^+ dermal dendritic cell is seen in the grenz zone. Indirect immunoperoxidase counterstained with haematoxylin, × 144

Fig. 2. Semiserial frozen sections of case 22 (parapsoriasis) stained with OKT_6 (2a) and HLA-DR (2b). Small clusters of OKT_6^+ and/or HLA-DR^+ epidermal Langerhans cells and dermal dendritic cells and HLA-DR^+ lymphocytes are seen. Indiret immunoperoxidase counterstained with haematoxylin, × 144

Fig. 3. Frozen section of case 40 (mycosis fungoides) stained for OKT_6. An epidermal area containing a large number of OKT_6^+ Langerhans cells alternates with an epidermal area in which only few OKT_6^+ Langerhans cells can be recognized. Indirect immunoperoxidase counterstained with haematoxylin, × 144

(Ralfkiaer et al. 1984; Van Hale and Winkelman 1985). Dermal dendritic cells are restricted to areas with a T-cell infiltrate (Geerts and Kaiserling 1985; Van Hale and Winkelman 1985; Wirt et al. 1985). Germinal centres, if present, may contain dendritic reticulum cells (Geerts and Kaiserling 1985; Ralfkiaer et al. 1984; Smolle et al. 1985; Wirt et al. 1985).

In skin lesions with a T-cell infiltrate increased numbers of epidermal Langerhans cells (Cox et al. 1986; Füllbrandt et al. 1983; Haynes et al. 1982; Holden et al. 1982; McKie 1982; McKie and Turbitt 1982; McMillan et al. 1982a; Ralfkiaer et al. 1985b; Van Hale and Winkelman 1985; Wirt et al. 1985) and dermal dendritic cells (Caorsi et al. 1982; Chu et al. 1982; Cox et al. 1986; Haynes

et al. 1982; McKie 1982; McMillan et al. 1981a, 1982a; Smolle et al. 1985; Takahashi et al. 1982; Tjernlund 1981; Tosca et al. 1986; Van Der Putte et al. 1986; Wirt et al. 1985; Wood et al. 1982) are present. Langerhans cells are found within Pautrier microabscesses (Füllbrandt et al. 1983; Haynes et al. 1982; Igisu et al. 1983; Jimbow et al. 1982; McMillan et al. 1982a; Matejka and Konrad 1983; Ralfkiaer et al. 1985b; Rowden et al. 1979; Tosca et al. 1986; Wood et al. 1982). Close apposition of T-lymphocytes to dendritic cells may occur both in epidermis and dermis (Caorsi et al. 1982; Füllbrandt et al. 1983; Jimbow et al. 1982; McKie and Turbitt 1982; Matejka and Konrad 1983; Meissner et al. 1983; Romagnoli et al. 1986; Rowden et al. 1979).

Our findings are in accordance with these data from the literature. Both epidermal Langerhans cells and dermal dendritic cells were more numerous in T-cell lesions than in B-cell lesions. We therefore conclude that the number and immunophenotype of epidermal Langerhans cells and dermal dendritic cells is not defined by the benign or malignant nature of the dermal lymphoid infiltrate but by its composition of B-cells or of T-cells.

In this study we also noted differences in the distribution of dendritic cells between B-cell lesions and T-cell lesions. In skin biopsies with a T-cell infiltrate, Langerhans cells were unevenly distributed throughout the epidermis. In skin lesions with an inflammatory infiltrate collections of dendritic cells and T-lymphocytes, admixed with small blood vessels gave rise to the formation of small clusters. The latter resemble secondary T-nodules of the paracortex of reactive lymph nodes, composed of $S_{100}{}^+$ and HLA-DR$^+$ dendritic cells intermingled with T-lymphocytes and vascular structures (Van den Oord et al. 1985). In the skin as well as in the lymph node, the majority of the T-cells in these aggregates bear the HLA-DR$^+$, $OKT_4{}^+$ phenotpye and thus correspond to activated helper/inducer T-cells (Evans et al. 1978; McMillan et al. 1981b; Reinherz et al. 1979).

The secondary T-nodules of the lymph node have been compared (Van den Oord et al. 1985) with dendritic cell-T-cell clusters observed in vitro during primary immune responses (Green and Jotte 1985; Inaba and Witmer 1984; Inaba and Steinman 1985, 1986). By analogy, we suggest that also the cutaneous cell aggregates represent an in vitro homologue of the clusters seen during in vitro experiments. In skin lesions with a T-cell tumour infiltrate, larger, more loosely arranged collections of epidermal Langerhans cells, dermal dendritic cells and tumour T-cells were noted. We can speculate that these larger aggregates stand for the malignant equivalent of the clusters found in inflammatory T-cell lesions.

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