Virchows Arch [Pathol Anat] (1984) 404:403–411

Virchows Archiv A

Multiple neuroendocrine carcinomas (so-called Merkel cell tumours) of the skin

Report on two cases with unique clinical course

D. Katenkamp and V. Wätzig

Institute of Pathology (Head: Prof. Dr. sc. med. Dr. h.c. mult. F. Bolck) and Clinic of Dermatology (Head: Prof. Dr. sc. med. H. Günther) of the Friedrich-Schiller-University of Jena, German Democratic Republic

Summary. Two neuroendocrine carcinomas of the skin (so-called Merkel cell tumours) are presented. In both cases multiple tumour nodules developed within the course of the disease. The light and electron microscopic observations correspond with the findings reported in other neuroendocrine carcinomas. As a variable morphological and clinical pattern for these tumours seems to exist we consider our two cases with their unique clinical picture to be an obviously infrequent variant of this tumour disease, we propose for it the term "multiple neuroendocrine carcinoma syndrome".

Key words: Neuroendocrine carcinoma of the skin – Merkel cell tumour – Multiple tumour nodules

Neuroendocrine carcinomas of the skin (so-called Merkel cell tumours) have been accepted as a clinicopathological entity. A review of the literature on this subject reveals a surprisingly broad scale of clinical and morphological findings suggesting the presence of several biological variants.

The majority of neuroendocrine carcinomas are said to be solitary, but there are some reports on several skin tumours occurring at the same or different times in the course of the disease (Abaci and Zak 1979; De Wolf-Peters et al. 1980; Sibley et al. 1980; Taxy et al. 1980; Silva and Mackay 1981; Pilotti et al. 1982; Tang et al. 1982; Rustin et al. 1983).

We have at our disposal 6 neuroendocrine skin carcinomas. Two of them showed a unique clinical picture due to the occurrence of an large number of skin nodules. Our report on these two cases is aimed at extending the knowledge of the possible biological spectrum of this disease.

Offprint requests to: Doz. Dr. sc. med. Detlef Katenkamp, Institut für Pathologie der Friedrich-Schiller-Universität Jena, DDR-6900 Jena, Ziegelmühlenweg 1

Patients and methods

Case 1. Male patient, 58 years old. At the beginning of the disease the patient noted several tumours in his skin. About 60 firm nodules developed within two years. Their diameters ranged between 0.3 and 4.2 cm, they were partly suffused and mobile. All regions of the skin were affected. However, the condition of the patient was good, lymph node swellings were not present. Metastases in the viscera could not be detected. The erythrocyte sedimentation rate was slightly elevated, but the other paraclinical findings were normal.

In order to cure the patient, nearly 50 tumors were removed surgically, but because of the appearance of many new tumours a polychemotherapeutic regimen (MOPP scheme) had to be started. Unfortunately, this had no clear influence on the further course of the tumor disease. In a state of despair the patient committed suicide. At autopsy no metastases in the inner organs or in lymph nodes were found, an alternative primary tumour was excluded.

Case 2. Male patient, 72 years old. For 1 year numerous skin nodules with diameters between 0.3 and 1.8 cm were observed (Fig. 1). The larger tumours were sometimes ulcerated. The patient could not give any information whether the disease started with a solitary tumour or whether there were multiple tumours from the beginning. All the time the patient has been feeling well. To date, about 40 tumours were removed by operation. After a DTIC-monotherapy the growth of tumours is reduced. At present, there is no evidence for extracutaneous dissemination. The paraclinical findings are not remarkable, no extracutaneous primary tumour has been detected.

The following stains were used for light microscopic examination: H&E, elastica-van Gieson, trichrome stain according to Goldner, Azan, Gomori's silver impregnation, argentaffin reaction according to Fontana-Masson, Grimelius' argyrophil reaction, Giemsa staining, Prussian blue, PAS reaction, Alcian blue at different pH values and Alcian blue/PAS.

For the electron microscopic examination tumour tissue was minced in 1 mm^3 cubes and fixed in 2.5% glutaraldehyde for 3 hs at 4° C (buffered with 0.1 M cacodylate buffer at pH 7.2), of semithin sections (stained by toluidine blue) and ultrathin sections (contrasted by uranyl acetate and lead citrate).

Results

Light microscopy

The carcinoma was generally localized in the dermis and adjacent subcutis, as a rule a tumour free zone of connective tissue remained between the neoplasm and the epidermis. A few large tumours showed ulceration due to their size.

The basic pattern of all carcinomas was characterized by a nest-, cluster- and trabecular-like arrangement of tumour cells, respectively (Fig. 2). Between the cell clusters (Zellballen-like – Fig. 2d) broad bundles of collagen were visible. Reticulin or collagen fibers could never be demonstrated amidst the individual cell complexes. In case 1 tumour cells occasionally formed cavities filled with erythrocytes suggesting an angioformative capacity (Fig. 2b). In the periphery of the carcinoma nodules an expanding, or more frequently invasive growth was observed.

As an important cytological feature the relative uniformity of the tumour cells must be emphasized. The nuclei were small and round to oval-shaped, they showed 1–3 distinct nucleoli which were never prominent, however. The chromatin was finely dispersed or visible in small lumps. The cytoplasm was found to be present in a moderate amount in case 1 and often without distinct cell borders in case 2. Argentaffin or argyrophil granules were not

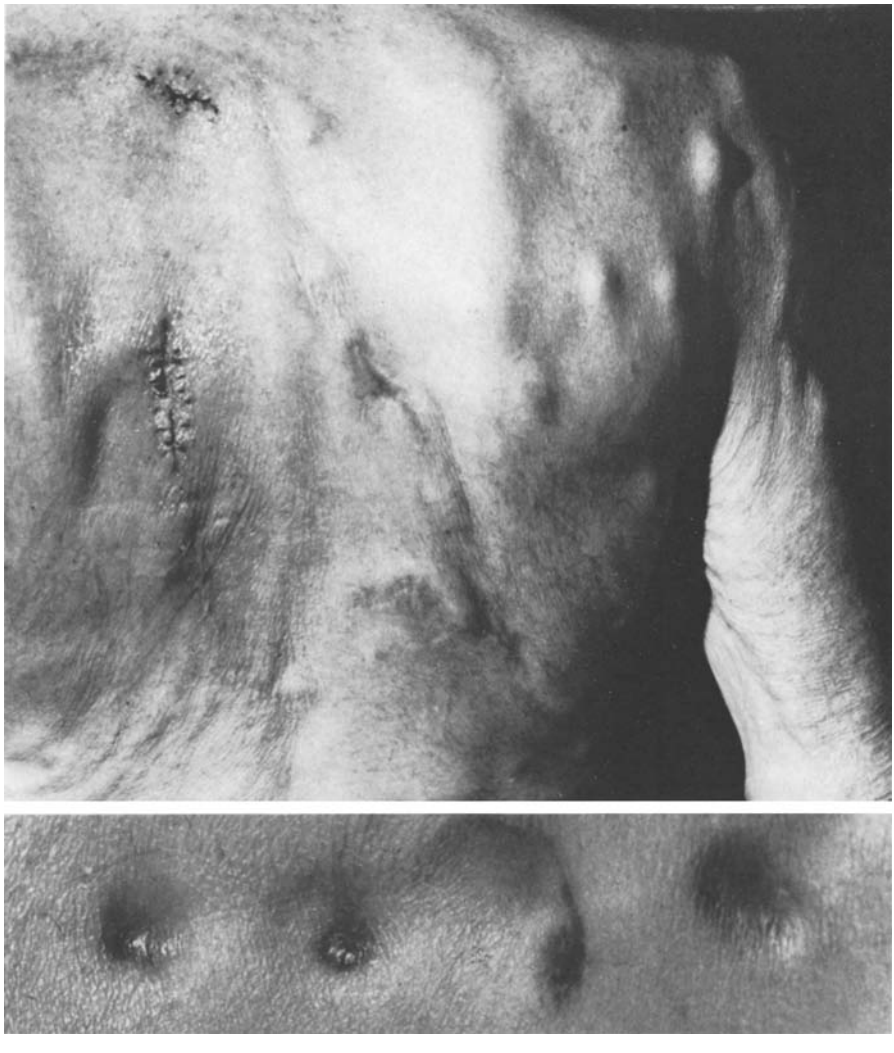

Fig. 1. Clinical appearance of the tumours. Note the intact epidermis which covers the tumour tissue

be seen in either case, melanin pigment was always absent. The Giemsa stain produced only a faint blue colour of the tumour cell cytoplasm. Mitoses were not to frequent.

Electron microscopy

In all tumour samples examined in the electron microscope there were similar findings, so that a summarizing description can be presented.

The tumour cells showed a round to polygonal shape and were rather densely packed. The cell membranes of adjacent cells often paralleled each other over a long distance, but no specialized cellular junctions (desmosomes

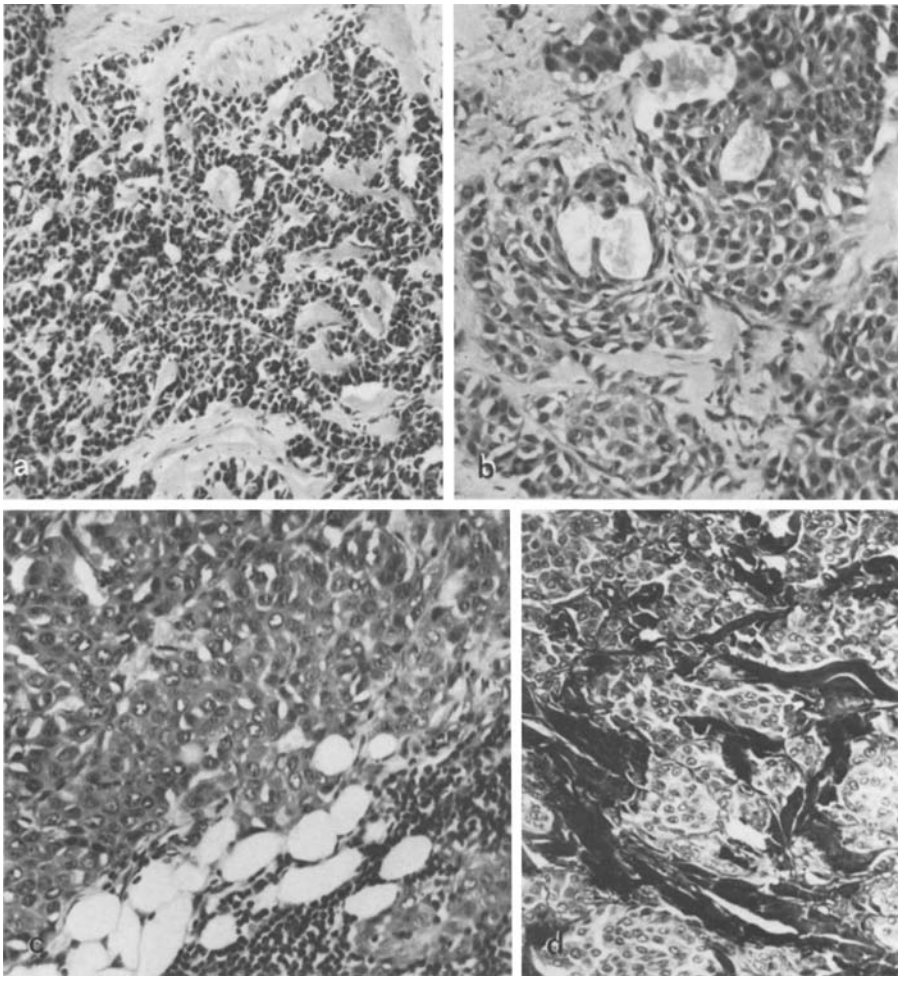

Fig. 2. Light microscopic picture of the tumour. **a** Trabecular arrangement of tumour cells (HE ×96). **b** Tumour cell clusters form three vessel-like spaces filled with erythrocytes (HE, ×150). **c** Note the uniform cytology and the invasive growth (HE, ×150). **d** Tumour cell clusters exhibit a "Zellballen" like picture. (Goldner, ×96)

or related structures) were to be seen. Occasionally, short and plump cellular protrusions were found.

The nuclei were round to oval and often displayed slight notchings. The heterochromatin was equally distributed, distinct nucleoli and nuclear bodies indicated nuclear activity. In the cytoplasm of many tumour cells we observed a well-developed Golgi complex, numerous vesicular structures and a moderate amount of mitochondria (Figs. 3, 4). In some tumour cells the number of the aforementioned organelles was reduced and free ribosomes and polysomes dominated the picture. In several cells some slender tubes of rough endoplasmic reticulum could be seen.

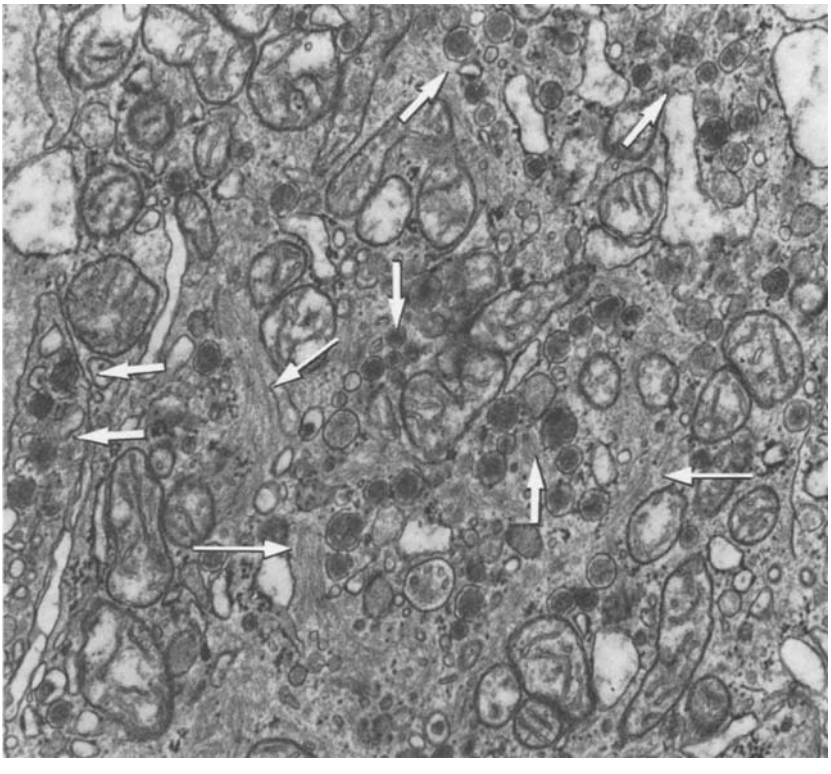

Fig. 3. Detail of a tumour cell. Mitochondria, small bundles of intermediate filaments (⇒) and numerous neurosecretory-type granules (⇒) with electron dense core, a narrow electron lucent halo and a bounding membrane can be seen. A basal lamina-like structure is present close to the cell (× 26,200)

In many cancer cells neurosecretory-type granules were to be found. They exhibited a narrow clear halo around a dense core and were membrane-bound (Figs. 3, 4). Their diameters ranged from 90 to 220 nm. Their number within a single cell was very variable. Not infrequently they were randomly distributed within the cytoplasm, sometimes an accumulation in the vicinity of cell membranes was obvious. In some tumour cells we identified small bundles of intermediate filaments which were often somewhat curved (Figs. 3, 4). Here and there scattered microtubules were encountered (Fig. 4b).

Tumour cell complexes were often enveloped by a basal lamina-like structure separating cancer cell complexes from the surrounding stromal connective tissue.

Discussion

Neuroendocrine carcinomas of the skin (so-called Merkel cell tumours) are cytologically uniform, may reveal an at least partially trabecular growth pattern and demonstrate neurosecretory granules as a pathognomonic trait

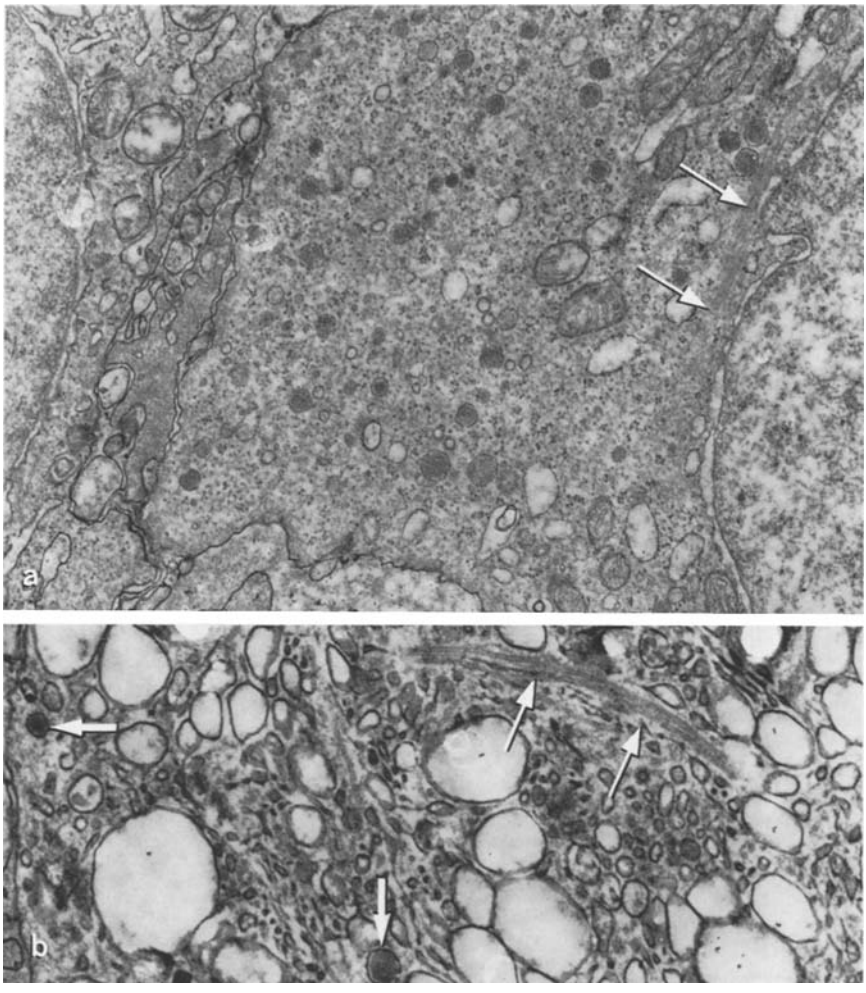

Fig. 4. **a** The cytoplasmic picture is dominated by ribosomes and polysomes as well as several neurosecretory-type granules. A small bundle of intermediate filaments is seen in a juxtanuclear position (→) (× 20,180). **b** Numerous vesicular structures, a few microtubuli (⇒) and neurosecretory granules (⇒) (× 32,100)

at ultrastructural level. These characteristics are visible in our two cases. Light microscopically, the differential diagnosis of a malignant melanoma or an anaplastic sweat gland carcinoma had to be considered, the electron microscopic findings excluded these diagnoses because neither premelanosomes and melanosomes, nor gland-like differentiations were to be seen. Furthermore, the autopsy in case 1 and the thorough clinical examinations in case 2 provided evidence for a primary skin tumour.

The capability of the tumour cells to form vessel-like spaces has not yet been described for neuroendocrine carcinomas as far as we know, but this phenomenon is well known in malignant melanomas, where tumour

cells are derived from the neuroectodermal tissue. The negative argyrophil and argentaffin reactions observed in our cases are compatible with the diagnosis of a neuroendocrine skin carcinoma and may be caused by formalin fixation (cp. also Toker 1972; Sibley et al. 1980; Silva and Mackay 1981; Kirkham and Isaacson 1983; Warner et al. 1983).

The large variability of the size of neurosecretory-type granules and their preponderately disseminated occurrence within the cellular cytoplasm in our cases clearly deviates from the findings in normal Merkel cells (Winkelmann 1977; Frigerio et al. 1983). In the literature there are some reports with similar observations (Tang and Toker 1978; Gould et al. 1980; Sidhu et al. 1980; Silva and Mackay 1981; Moya et al. 1982; Nakashima et al. 1983). The lack of specialized cellular junctions in our material was also noted by De Wolf-Peters and coworkers (1980) although in most reports they have been demonstrated. We recognized a basal lamina-like formation, other authors did not find such a structure (Sidhu et al. 1980). The two tumours presented here reveal features of an endocrine differentiation but do not give any evidence of their histogenesis.

At present, Merkel cells are the only known endocrine cells in the epidermis and dermis. Thus a close relationship of primary neuroendocrine skin carcinomas and Merkel cells has bee postulated (Tang and Toker 1978). Unfortunately, immunohistochemistry could not confirm such an origin due to the absence of a specific Merkel cell marker. However, there are good arguments for the assumption of a development of neuroendocrine carcinomas from multipotent epithelial precursor cells which are able to differentiate into endocrinetype cells. We feel the term "neuroendocrine carcinoma of skin" is the best designation at present and preferrable to "Merkel cell tumour" (cf. also Rosai 1982).

The hypothesis of a multipotent precursor cell could also explain the light and electron microscopic differences documented for individual tumours in the literature, including the remarkably variable diameters of neurosecretory granules. In supporting this hypothesis we have considered reports on the detection of endocrine cells in basal cell and squamous cell carcinomas (Macadam 1978; Eusebi et al. 1979; Gomez et al. 1981). Furthermore, some authors found squamous cell differentiations in otherwise typical neuroendocrine skin carcinomas (Tang and Toker 1978; Sidhu et al. 1980; Gomez et al. 1981; Tang et al. 1982; Fetissof et al. 1983; Frigerio et al. 1983).

From the mainly dermal localization it is reasonable to assume that the tumour might be an adnexal lesion which develops from multipotent precursor cells. We feel that the multiple tumour nodules in our cases may be regarded as an analogy to the occasionally multicentric appearance of certain basal cell carcinomas. In this connection the occurrence of basal cell carcinomas together with neuroendocrine carcinomas should be mentioned (Moya et al. 1982).

Whilst neuroendocrine skin carcinomas are said to prevail in the female sex (Cremer and Totovic 1983), our two patients with multiple tumours were male.

In summary, neuroendocrine skin carcinomas present a range of morphological pictures (cp. Tang et al. 1982) with neurosecretory granules regarded as the unifying feature (Hübner et al. 1983; Warner et al. 1983). With a variable morphology these tumours may take different clinical courses. We report here two cases with multiple tumour nodules constituting an obviously infrequent variant of the disease. Only Abaci and Zak (1979) have described a similar disseminated distribution, but they observed only 7 tumours. It is impossible to decide whether the tumour multiplicity is a synchronous or metachronous multicentric tumour development, or metastatic growth. We therefore propose the term "syndrome of multiple neuroendocrine carcinomas of the skin".

References

Abaci IF, Zak FG (1979) Multicentric amyloid containing cutaneous trabecular carcinoma. Case report with ultrastructural study. J Cutan Pathol 6:292–303

Cremer H Totovic V (1983) Der Merkelzell-Tumor der Haut. Licht- und elektronenmikroskopische Untersuchung an fünf Fällen. Pathologe 4:287–293

De Wolf-Peters C, Marien K, Mebis J, Desmet V (1980) A cutaneous APUDoma or Merkel cell tumor? A morphologically recognizable tumor with a biological and histological malignant aspect in contrast with its clinical behavior. Cancer 46:1810–1816

Eusebi V, Mambelli V, Tison V, DeLellis R, Betts CM (1979) Endocrine differentiation in basal cell carcinoma. Tumori 65:191–199

Fetissof F, Arbeille-Brassart B, Colombat Ph, Lorette G, Monegier du Sorbier Ch, Jobard P (1983) Tumeur à cellules de Merkel. Ann Pathol 3:285–291

Frigerio B, Capella C, Eusebi V, Tenti P, Azzopardi JG (1983) Merkel cell carcinoma of the skin: The structure and origin of normal Merkel cells. Histopathology 7:229–249

Gomez LG, Dimaio SM, Silva EG, Mackay B (1981) The association between neuroendocrine (Merkel cell) carcinoma and squamous carcinoma of the skin. Lab Invest 44:24A

Gould VE, Dardi LE, Memoli VA, Johannessen JV (1980) Neuroendocrine carcinomas of the skin: Light microscopic, ultrastructural, and immunohistochemical analysis. Ultrastruct Pathol 1:499–509

Hübner G, Remberger K, Pielsticker K (1983) Neuroendocrine carcinoma (Merkel cell tumour) of the skin. Pathologe 4:212–218

Kirkham N, Isaacson P (1983) Merkel cell carcinoma: Report of three cases with neurone-specific enolase activity. Histopathology 7:251–259

Macadam RF (1978) An electron-microscopic study of basal cell carcinoma. J Pathol 126:149–156

Moya CE, Guarda LA, Dyer GA, Silva EG, Shah S (1982) Neuroendocrine carcinoma of the skin in a young adult. Am J Clin Pathol 78:783–785

Nakashima N, Goto K, Takeuchi J, Maeda H (1983) Case report of neuroendocrine carcinoma of the skin, histochemical and electron microscopic study. Virchows Arch A 401:261–270

Pilotti S, Rilke F, Lombardi L (1982) Neuroendocrine (Merkel cell) carcinoma of the skin. Am J Surg Pathol 6:243–254

Rosai J (1982) On the nature and nomenclature of a primary small cell carcinoma of the skin exhibiting endocrine (? Merkel cell) differentiation. Am J Dermatopathol 4:501–505

Rustin MHA, Chambers TJ, Levison DA, Munro DD (1983) Merkel cell tumour: report of a case. Br J Dermatol 108:711–715

Sibley RK, Rosai J, Fourcar E, Dehner LP, Bosl C (1980) Neuroendocrine (Merkel cell) carcinoma of the skin. A histologic and ultrastructural study of two cases. Am J Surg Pathol 4:211–221

Sidhu GS, Feiner H, Flotte TJ, Mullins JD, Schaefler K, Schultenover SJ (1980) Merkel cell neoplasms: Histology, electron microscopy, biology and histogenesis. Am J Dermatopathol 2:101–119

Silva E, Mackay B (1981) Neuroendocrine (Merkel cell) carcinoma of the skin: An ultrastructural study of nine cases. Ultrastruct Pathol 2:1–9

Tang CK, Toker C (1978) Trabecular carcinoma of the skin. An ultrastructural study. Cancer 42:2311–2321

Tang CK, Toker C, Nedwich A, Zaman ANF (1982) Unusual cutaneous carcinoma with features of small cell (oat cell-like) and squamous cell carcinomas. A variant of malignant Merkel cell neoplasm. Am J Dermatopathol 4:537–548

Taxy JB, Ettinger DS, Wharam MD (1980) Primary small cell carcinoma of the skin. Cancer 46:2308–2311

Toker C (1972) Trabecular carcinoma of the skin. Arch Dermatol 105:107–110

Warner TFCS, Uno H, Hafez GR, Burgess J, Bolles C, Lloyd RV, Oka M (1983) Merkel cells and Merkel cell tumors: Ultrastructure, immunohistochemistry and review of the literature. Cancer 52:238–245

Winkelmann RK (1977) The Merkel cell system and a comparison between it and the neurosecretory or APUD cell system. J Invest Derm 69:41–46

Accepted July 16, 1984