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# Case report of neuroendocrine carcinoma of the skin, histochemical and electron microscopic study

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**Summary.** A rare case of neuroendocrine carcinoma of the skin in a 83-year-old male Japanese was reported. Histological, electron microscopical and cytological studies were performed on the surgically removed tumor tissue and the cultured tissue. The tumor occurred at the junction of the dermis and subcutaneous tissue of the right elbow, and spread to the right brachial region and axilla. Histologically, the tumor consisted mostly of small anaplastic cells, closely resembling lymphocytes. They showed a characteristic uniformity without rosette or trabecular formation in the usual histological sections, but an epithelial-like arrangement of tumor cells was readily observable both in the tissue culture and imprint preparations. Grimelius' stain was weakly positive in the periphery of the cytoplasm. Neuron Specific Enolase (NSE) activity was high both in the serum and in the tumor mass. No gastro-entero-pancreatic hormones were detected. Electron microscopically, membrane-bound granules of neurosecretory type, 90 to 170 nm in diameter were observed in the cytoplasm. These granules were characteristically distributed along the periphery of cytoplasm beneath the plasma membrane and in clusters in the cell processes. The tumor cells had sparse rudimentary desmosome-like junctions and a few cytoplasmic finger-like projections. Either a neurogenic or APUD cell origin of the tumor was suspected. The serum NSE value, suggesting to be a neurogenic origin before the histological examination in the present case, is considered to be a valuable marker substance for screening and therapeutic monitoring of neurogenic tumors.

**Key words:** Neuroendocrine carcinoma – Neuron specific enolase

Neuroendocrine carcinoma of the skin is extremely rare. To the authors' knowledge, only 11 cases have been reported in detail in the literature. The

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tumor generally arises in the dermis or the neighboring subcutaneous tissue of an elderly person without a definite sex predilection, but possibly with a slight female predominance. Toker (1972), the first reporter of the tumor, held that it arose from a primitive sudoriferous tissue, but he and his co-worker (Tang and Toker 1978) subsequently indicated that it might be derived from Merkel cell. Sibley et al. (1980) reiterated the same origin. This opinion as to the origin is based on an ultrastructural similarity of configuration between tumor cells and Merkel cells. However, there is an important difference between them: Merkel cells are commonly found in the basal layer of the epidermis whereas the neuroendocrine tumor is found in the dermis or in the subcutaneous tissue, and not in the epidermis. Thus, origin of neuroendocrine carcinoma of the skin requires further elucidation.

The present study reports the histopathological and electron microscopical findings in a rare case of neuroendocrine carcinoma of the skin, which is very similar to the cases hitherto reported. The origin of the tumor cell is briefly discussed.

## Materials and methods

For light microscopical examination the tumors obtained from surgical excisions and autopsy were fixed in buffered formalin, embedded in paraffin and sectioned. The tissue sections were stained by the following dyes; H-E, periodic acid Schiff's reagent, Alcian blue, AZAN, orcein, silver impregnation, Fontana-Masson and Grimelius. Imprint preparations from fresh cut surface of tumor were made and stained with Giemsa and Grimelius.

For E-rosette examination pieces of tumor were minced and the free tumor cells obtained were washed three times with phosphate buffer saline (PBS) and centrifuged. The sediment was mixed with PBS, fetal calf serum and an equal volume of sheep red blood cell. The tubes containing the mixture were centrifuged at room temperature for 5 minutes and then incubated in an ice bath for 60 minutes. The tubes were then gently rocked to resuspend the cells on a slide glass, and the rosettes were counted. The peroxidase reaction was also carried out in order to confirm that the cells were not of myelogenic origin.

For electron microscopic examination some tissues were fixed in 2% Millonig's phosphate buffered osmium tetraoxide, and embedded in Epon 812. Thin sections were observed under a Hitachi electron microscope operating at 75 KV. Pieces of tumor obtained by biopsy were grown in RPMI 1640 medium, supplemented with 10% fetal calf serum, kanamycin (100 mg/100 ml) and penicillin (1,000 U/100 ml). Immunoperoxidase study (PAP method) for gastro-entero-pancreatic (GEP) hormones was made by the same procedures as described by Takeda et al. (1982).

## Case report

Early in June 1981, a 83-year-old Japanese male consulted his physician because of a swelling in the soft tissue of the right elbow. Because of a traffic accident, he had had his leg amputated at the femur, but otherwise was relatively good health. The lesion was freely movable but fixed to the skin.

On 8 June, a partial biopsy was performed. A nodular tumor, about $2 \times 2$ cm in diameter, was whitish, medullary and well demarcated from the surrounding dermis. The tumor was markedly cellular, almost completely replacing the dermis. Histopathologically, it proved to be a poorly differentiated malignant tumor and was tentatively diagnosed as lymphoma.

On 5 August, the remaining tumor, $5 \times 4 \times 3$ cm in diameter, was excised. Macroscopically, it was found in the soft tissue accompanied with local adhesion to the muscular fascia, and the cut surfaces were gray and cellular, with brown areas of haemorrhage. In November,

**Table 1.** Laboratory examinations

| | | | |
|---|---|---|---|
| WBC | $10.3 \times 10^3$ | Total cholesterol | 165 mg/dl |
| RBC | $466 \times 10^4$ | $\beta$-lipo | 480 mg/dl |
| Hb | 14.3 g/dl | TG | 173 mg/dl |
| Ht | 42.4% | Phospholipid | 155 mg/dl |
| | | HDL-cholesterol | 36 mg/dl |
| Hemogram | | TC/HDL-C rate | 4.58 |
| Stab | 23% | | |
| II | 22% | Protein fraction | |
| III | 24% | Al | 48.9% |
| IV | 3% | $\alpha_1$-gl | 6.7% |
| V | 0% | $\alpha_2$-gl | 10.6% |
| Ly | 25% | $\beta$-gl | 11.3% |
| Mo | 3% | $\gamma$-gl | 22.2% |
| Total p. | 7.1 g/dl | Immunoglobulin | |
| Albumin | 2.9 g/dl | G | 2040 mg/dl |
| TTT | 9.3 | A | 390 mg/dl |
| ZTT | 15.6 | M | 170 mg/dl |
| CCLF | (+)→(−) | | |
| GOT | 11 Karmen Unit | CRP 5+ →(−) | |
| GPT | 7 Karmen Unit | RA (−) | |
| ALP | 6.6 K-A Unit | | |
| LDH | 292 IU/l | ESR | |
| CHE | 0.59 pH | 30′ 60′ 120′ | |
| Bil | 0.6 mg/dl | 90 120 140 mm | |
| LAP | 115 G-P Unit | | |
| r-GTP | 20 mU/ml | AFP 2 ng/ml | |
| Urea N | 28 mg/dl | CEA 1.8 ng/ml | |
| Uric acid | 7.7 mg/dl | | |
| Na | 146 mEq/dl | BMG 4.7 ng/l | |
| K | 4.4 mEq/dl | Serum ferritin | 19.8 ng/ml |
| Cl | 104 mEq/dl | | |
| Ca | 4.9 mEq/dl | | |
| Creatinine | 1.1 mg/dl | | |
| P | 3.4 mg/dl | | |

right radial nerve palsy was noticed, and the tumor recurred simultaneously in the operation scar and was re-excised. On 7 December, the tumor recurred in the right upper arm on the posterior aspect and was removed. The tumor located chiefly in the soft tissue and the brachial muscle, and encroached on the radial nerve.

On 21 December, the tumor ($3 \times 3$ cm) had recurred in the axillary fossa and was partially resected. It had enlarged rapidly to become the size of an adult fist within about 2 weeks.

On 3 January 1982, treatment beginning with Oncobin 2 mg, Endoxan 500 mg and prednisone 30 mg at a total dose of 8 mg, 2,000 mg and 120 mg, respectively, for about a month, resulted in a dramatic regression of the tumor.

In the middle of April, however, the tumor recurred in the dermis and the soft tissue of both the right upper extremity and axilla; by a 6th operation it was partially removed, followed by chemotherapy with the same agents and dosage indicated, resulting again in a seemingly complete remission.

Early in August, the tumor recurred, and chemotherapy was continued, but gradually became less effective. Gradual deterioration occurred along with dyspnea before death on 29 September.

**Table 2.** Results of hormone assay

| Hormone | Value | Normal |
|---|---|---|
| Metanephrine (urine) | 0.10 mg/day | 0.01–0.13 mg/day |
| Normetanephrine (urine) | 0.22 mg/day | 0.04–0.38 mg/day |
| VMA (urine) | (−) | |
| HVA (urine) | 2.0 mg/day | 0.3–6.6 mg/day |
| Catecholamines (urine) | 85.7–163.0 μg/day | 29–137 μg/day |
| Cortisol (serum) | 10.3, 8.6 μg/dl | 3.7–13.0 μg/dl |
| Glucagon (serum) | 30 pg/ml | 40–180 pg/ml |
| ACTH (serum) | 54 pg/ml | 10–90 pg/ml |
| Aldosterone (serum) | 70.8 pg/ml | 10.9–62.7 pg/ml |
| Adrenaline (serum) | 0.01 ng/ml | 0.12 ng/ml |
| Noradrenaline (serum) | 0.31 ng/ml | 0.06–0.45 ng/ml |
| $T_3$ (serum) | 29.0% | 23.2–32.6% |
| $T_4$ (serum) | 7.2 μg/dl | 5.0–13.0 μg/dl |
| Triiodothyronine (serum) | 0.71 μg/ml | 0.8–1.9 μg/ml |
| TSH (serum) | 3.6 μU/ml | 10 μU/ml |
| Insulin | 17.7 μU/ml | 20 μU/ml |

Laboratory data were unremarkable (Table 1). Chest, abdominal viscera and other organs were negative with examination by X-photo, CT-scan and gallium syncigram. A hormone assay revealed normal values as shown in Table 2.

At autopsy, tumors were found in the subcutaneous tissue of the right side of the brachial region, axilla and clavicles. These tumors ranged in size from an infantile fist to that of an adult or larger; they consisted of a conglomeration of tumor nodules from a cherry to a walnut (Fig. 1). Another tumor, $1.0 \times 1.2$ cm in diameter, was buried in the parenchyma of the pancreatic tail (Fig. 2). The trachea and bronchi on both sides were filled with viscous mucus, and the right lung showed an atelectasis with cryptococcal infection. A right hydrothorax (containing 450 ml serous fluid) was found. In the other thoracic and in the abdominal viscera, no significant changes were observed.

*Light microscopy*

Specimens of tumors obtained by six biopsies were examined. The original tumor is observed in the dermis and in the neighboring soft tissue, and even though grossly well-circumscribed, microscopically it is not. The epidermis is uninvolved throughout. Histopathological findings of the 6 different tumors bear a striking resemblance to each other. The tumor cells infiltrate the surrounding subcutaneous adipose tissue. The tumor cells show little cytoplasm, a poorly defined outline, and are about 7.5–12 μm in diameter; they are characteristically uniform in appearance and arranged in compact masses. Their uniformly round or oval nuclei have diffuse fine chromatin with one to three indistinct nucleoli (Fig. 3). Mitotic figures are numerous, with over 5 mitoses per highpower field. Rosettes or acini are absent. The cells are negative for PAS or Alcian blue. Stains for reticulin reveal a moderate number of fine reticulin fibers separating the tumor tissue into many compartments. No granules with Fontana-Masson stain are observed, and in Grimelius' argyrophil stain the cytoplasm of the tumor cells is stippled peripherally (Fig. 4). No E-rosette formation is noted. The peroxidase reaction is negative. An imprint preparation from the fresh-cut surface of the tumor shows round cell nuclei with 3–4 indistinct nucleoli. The cells, measuring approximately 12–18 μm in diameter and with scanty cytoplasm, are basophilic and often attach to one another to show an epithelial-like arrangement (Fig. 5). In Grimelius' staining of the imprint preparation fine granules are also found in the cytoplasm peripherally.

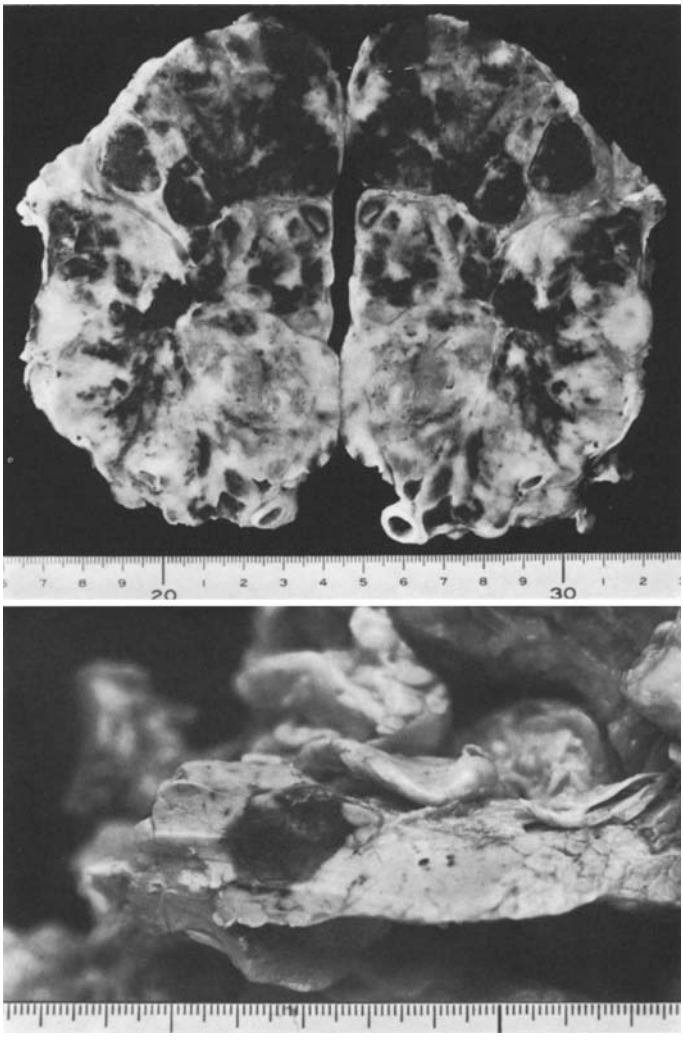
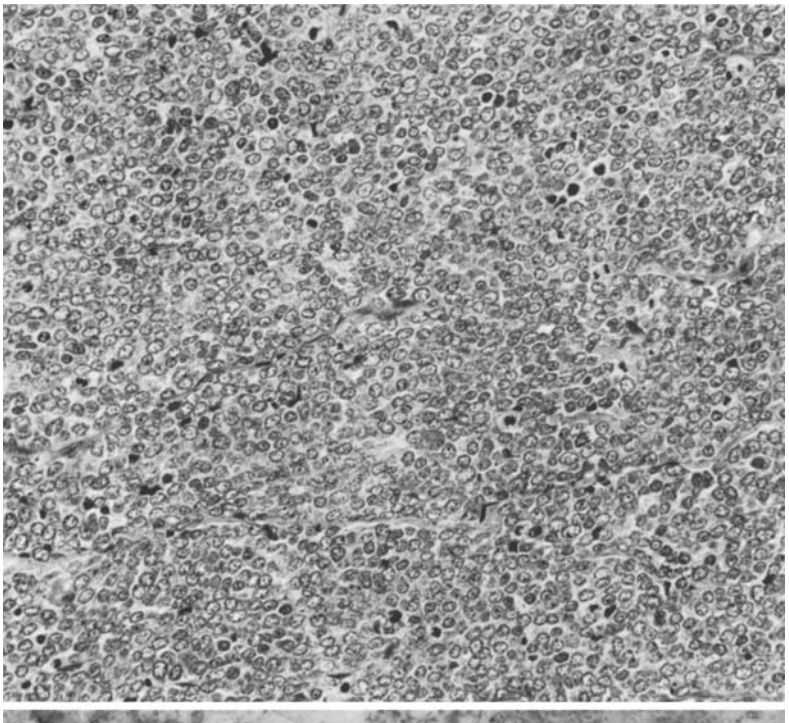


**Fig. 1.** A cross section of the tumor in the axilla, consisting of a conglomeration of haemorrhagic tumor nodules

**Fig. 2.** A cross section of the pancreas. A haemorrhagic tumor nodule, is found in the parenchyma of the pancreatic tail

Histological findings in the tumors obtained from autopsy were nearly the same as the ones from biopsy. The tumor of the pancreatic tail was haemorrhagic and not well circumscribed, with a marked lymphatic involvement. Either exocrine and endocrine glands were observed scattered within the tumor tissue. Considerable search through multiple sections of the trachea, the hylus of the lung, both lungs, and the liver was made to find the route of metastasis to the pancreas, but no tumor was found.



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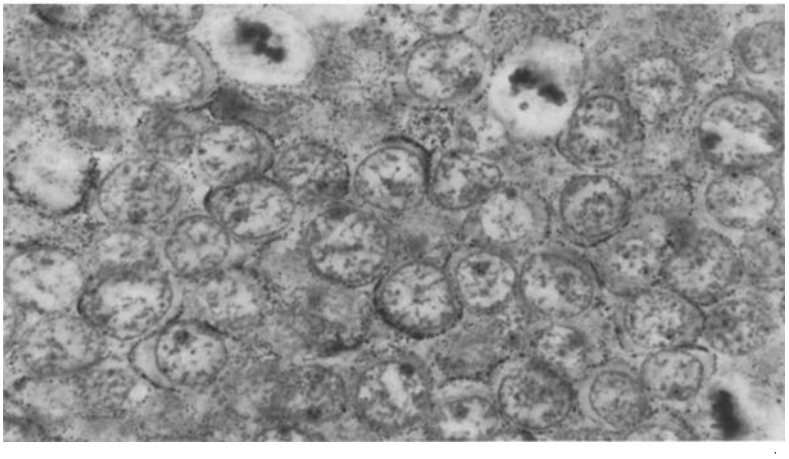

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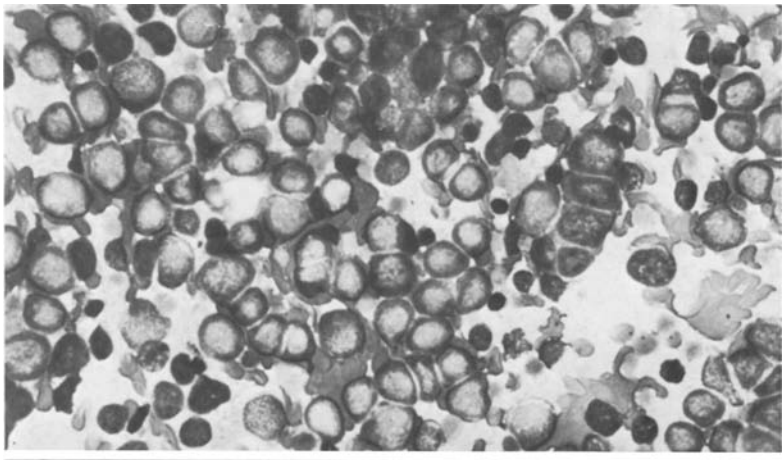
**Fig. 3.** Microscopic section of the tumor tissue, showing the tumor cells with little cytoplasm. They are uniform in appearance and arrange in compact masses (HE, 250:1)

**Fig. 4.** Microscopic section of the tumor tissue, showing the tumor cells stippled with fine argyrophil granules peripherally (Grimelius stain, 1,000:1)



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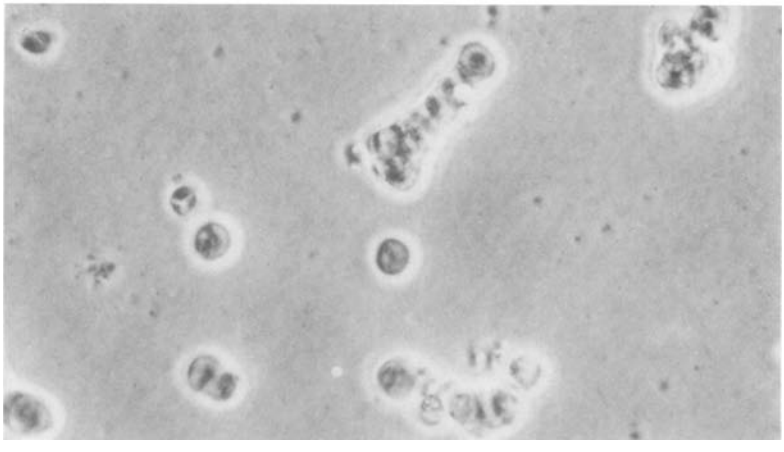

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**Fig. 5.** Imprint preparation from a fresh-cut surface of the tumor, showing an epithelial-like arrangement (Giemsa's stain, 400:1)

**Fig. 6.** Tissue culture of the tumor, showing an epithelial-like arrangement (Phase contrast microscopy, 400:1)

*Electron microscopy*

The tumor consists of relatively compactly arranged electron-lucent polyhedral cells interspersed by electron-dense cells (Fig. 7). Each cell has a moderate amount of cytoplasm containing numerous free mono- and polyribosomes and small amounts of rough-surfaced endoplasmic reticulum. Many small, rod-shaped mitochondria are seen, occasionally in clusters. The Golgi-apparatus is generally well developed. The tumor cells have a round nucleus with fine nuclear chromatin dispersed diffusely, and a small amount of heterochromatin condensed along the nuclear membrane, with several indistinct nucleoli. Intercellular junctions between tumor cells are relatively rare, and the cells attach to each other by sparse rudimentary desmosome-like junctions. No cytoplasmic fibrillar attachment to the desmosomes is noted.

Membrane-bound granules of neuro-secretory type, 90 to 170 nm in diameter (mean, 110 nm), are observed in the cytoplasm of most tumor cells (Figs. 7 and 8). The granule

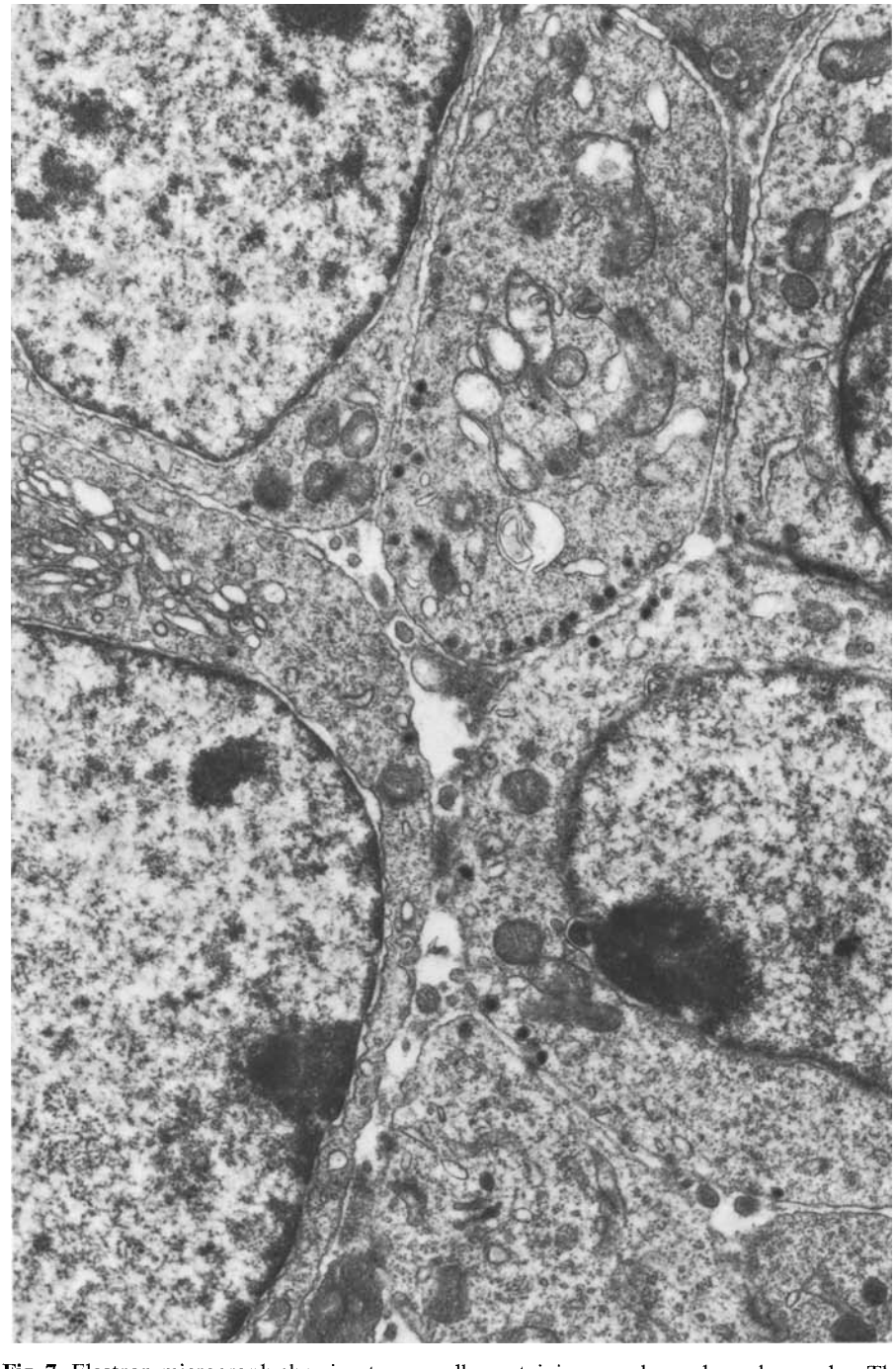
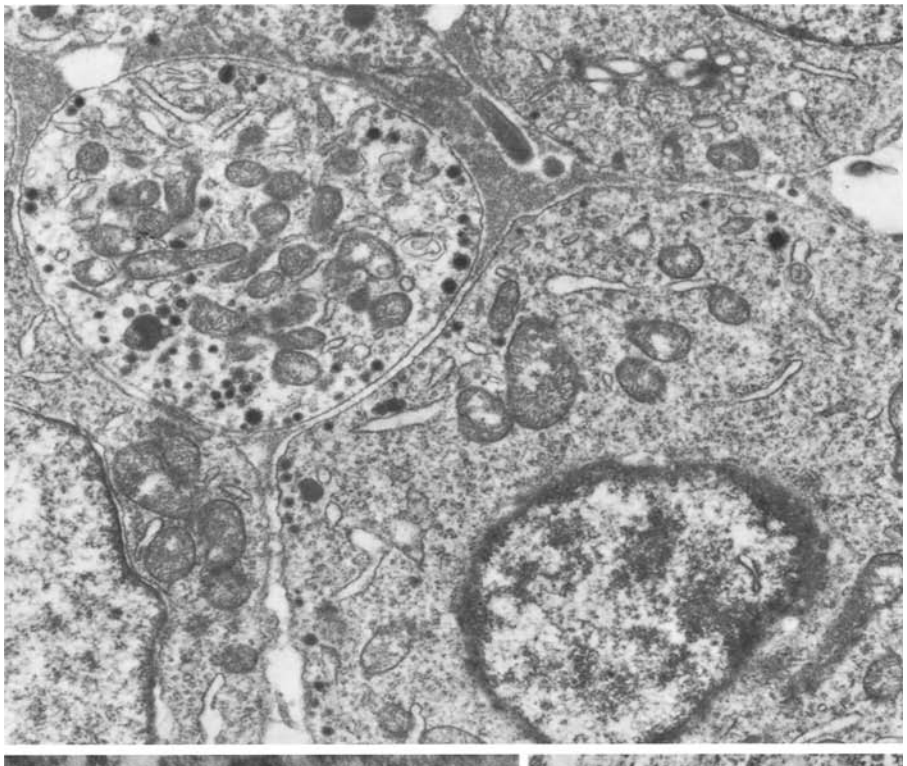


**Fig. 7.** Electron micrograph showing tumor cells containing membrane-bound granules. They tend to distribute along the periphery (10,500:1)



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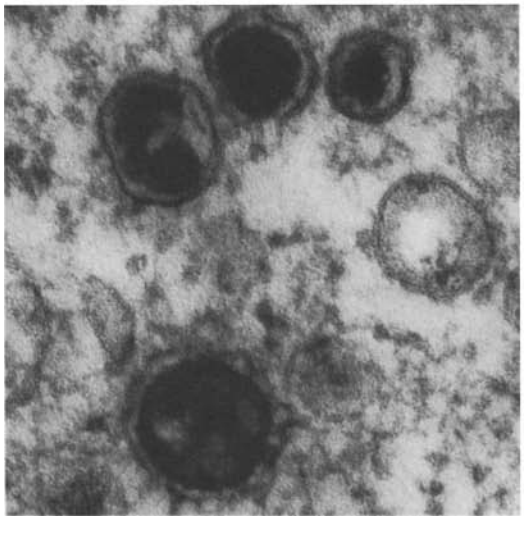

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**Fig. 8.** Electron micrograph showing tumor cells containing many membrane-bound granules in the cytoprocess (7,500:1)

**Fig. 9.** Electron micrograph showing membrane-bound granules in higher magnification (120,000:1)

**Fig. 10.** Electron micrograph showing the finger-like projections (30,000:1)

cores vary in electron density, surrounded by a clear space about 8 nm in width (Fig. 9). They tend to distribute along the periphery beneath the plasma membrane and in clusters in the cell processes (Figs. 7 and 8), which have no microtubules (the major hallmark of neuroblastoma), and seem to originate from Golgi saccules as relatively electron light vesicles. Their proximity to the cytoplasmic membrane explains their abrupt increase in electron density. The cell has occasionally a few cytoplasmic finger-like projections, 150 nm in diameter 530 nm in length, devoid of all organelles (Fig. 10). No intranuclear rodlet described by Fortman (1973) and Winkelmann (1977) is observed in the tumor cells. Melanosomes or premelanosomes are not identifiable in the tumor cells.

*Tissue culture*

On the 5th and 6th surgical specimens respectively, pieces of tumor fragment were inoculated into plastic bottles containing RPMI tissue culture medium. The majority of tumor cells were floating, and did not adhere to each other though some cells seemed to show an epithelial-like arrangement (Fig. 6). On a fibroblastic sheet they survived longer, but active growth was not observed, and died away about 3 weeks later.

*Neuron specific enolase (NSE)*

Table 3 shows the results of the enolase assay performed on the present case. Before chemotherapy (January 8, 1982) NSE was 30.0 ng/ml in the serum, and after chemotherapy (February 12, and 19, when the tumor was almost completely regressed), it was 2.12 and 2.24 ng/ml, respectively, (normal: under 7 ng/ml). Distribution of $\alpha\alpha$, $\alpha\gamma$, and $\gamma\gamma$ forms of enolase was also investigated in various tumor tissues and kidney. NSE ($\gamma\gamma$) content was 0.4 ng/mg protein in the tumor mass of the present case, and higher in pheochromocytoma, ganglioneuroblastoma and ganglioneuroma but NSE was virtually undetected in normal kidney, rhabdomyosarcoma, nephroblastoma, and adrenocortical adenoma. In paraffin-embedded thin sections NSE of tumor cells were positively stained by an immunoperoxidase technique using an antiserum for rat NSE.

**Table 3.** Contents of neuron specific enolase in serum

| | | |
|---|---|---|
| January 8 | (before chemotherapy) | 30.0 ng/ml |
| February 12 | (after chemotherapy) | 2.12 ng/ml |
| February 19 | (after chemotherapy) | 2.24 ng/ml |

Distribution of $\alpha\alpha$, $\alpha\gamma$ and $\gamma\gamma$ forms of enolase in various tumor tissues

| Tumor tissues | Enolase isozyme (ng/mg protein) | | |
|---|---|---|---|
| | $\alpha\alpha$ | $\alpha\gamma$ | $\gamma\gamma$ |
| 1. Hygroma | 5.66 | 0.85 | 0.0 |
| 2. Rhabdomyosarcoma | 5.89 | 0.35 | 0.0 |
| 3. Kidney | 17.48 | 0.51 | 0.0 |
| 4. Nephroblastoma | 5.46 | 0.21 | 0.0 |
| 5. Adrenocortical adenoma | 9.53 | 1.89 | 0.0 |
| 6. Adrenocortical carcinoma | 0.48 | 0.78 | 0.09 |
| 7. Pheochromocytoma | 6.22 | 7.45 | 1.33 |
| 8. Ganglioneuroblastoma | 3.41 | 5.66 | 1.62 |
| 9. Ganglioneuroma | 0.91 | 2.00 | 1.46 |
| 10. Present case | 8.04 | 6.71 | 0.44 |

By Courtesy of Dr. Kanefusa Kato and Dr. Yukio Ishiguro

*GEP hormone detection by immunoperoxidase method.* The tumor of the right elbow and the pancreatic tail was examined for ACTH, calcitonin, secretin, gastrin, motilin, glucagon, somatostatin, vasoactive intestinal peptide (VIP) by immunoperoxidase techniques (PAP) in histological sections, but no hormone producing activity was detected in the tumor cells.

## Discussion

A rare case of neuroendocrine carcinoma is presented which arose from the dermis or subcutaneous tissue of the right elbow. To date, twelve similar cases (Toker 1972; Tang and Toker 1978; Sibley et al. 1980; Iwasaki et al. 1981), including the present case, have been reported with relatively detailed descriptions. The age ranged from 65 to 92 years old, with an average of 76 years old. The ratio of male to female was 5:7. The tumor occurred predominantly on the face and in the upper extremity. The size of the tumor removed at the first operation was 1–3 cm in diameter. The tumor was located in the dermis or in the neighboring muscles. In seven cases, a rosette and/or trabecular structure were observed in the tumor tissues. In all cases Fontana-Masson stain was negative, and the Grimelius stain positive for Iwasaki's and the present case, in both of which the granules were inconspicuous and characteristically located in the periphery of the cytoplasm.

Ultrastructural examination was carried out in seven cases. Cored vesicles ranging from 90 nm to 250 nm in diameter were observed in each case. They were distinctly observed in the subcytoplasmic membrane or in the cytoplasmic processes in clusters. Microtubules were not found in the processes. A junctional apparatus was not evident; if any were present they were small and rudimentary in development. Free ribosomes were abundant except for 2 cases reported by Sibley et al. (1980) and the endoplasmic reticulum was generally poorly developed. One of Tang's cases and the present case rarely had a finger-like cytoplasmic process resembling microvilli. Nuclei were generally round with some inconspicuous nuceoli.

The Merkel cell, one of the members of the APUD cell series, has been considered to be the origin of the tumor by some authors (Tang and Toker 1978; Sibley et al. 1980). Merkel cells are usually found singly or in a group in the basal layer of the epithelium or clustered in rete ridges (Hashimoto 1972); they have a close connection with a neurite of an intraepidermal sensory nerve ending (Hashimoto 1972; Winkelmann and Breathnach 1973). Electron microscopically they resemble neuroendocrine carcinoma of the skin in many respect; Merkel cells have cored vesicles about 90–100 nm in diameter, a small number of rudimentary desmosomes connecting to the surrounding keratinocytes, and occasionally a few finger-like cytoplasmic processes wedging into the surrounding keratinocytes (Winkelmann 1977). However, the location of the tumor cells seems to be different from that of Merkel cells. Merkel cells are mostly situated within the epidermis (Hashimoto 1972; Winkelmann 1979; Iggo and Muir 1969), but in all 12 cases the tumors arose in the dermis, the epidermis being free of tumor

in primary lesions. Although the Merkel cell was reported to locate in the dermis (McGavran 1964) and soft tissue in association with the nerve fibers (Breathnach and Robins 1970), it is very rare to find them there, especially in an adult (Winkelmann 1977). If the Merkel cell is the origin of these tumors, how does one explain the differences in location? Nuclei of Merkel cell were usually multilobular (Hashimoto 1972; Winkelmann and Breathnach 1973), whereas those of the neuroendocrine carcinoma of the skin were almost always round or oval.

According to the APUD concept, the neuroendocrine carcinoma of the skin is one variant of neuroblastoma, and there might be only a little difference between these two tumors arising from the same trunk – the neural crest. Mackay et al. (1976) reported nine cases of adult neuroblastomas, some of which resembled the neuroendocrine carcinoma in the light and electron microscopic findings. The tumor showed a rosette or trabecular structure easily found by light microscopy. Recently, the nature and nomenclature of primary skin carcinoma exhibiting endocrine differentiation was discussed (Toker 1982; Rosai 1982; Urmacher 1982; Sidhu 1982; Rywlin 1982; Stern 1982). Toker (1982) considered that the tumor might originate from the sweat gland.

Schmechel et al. (1978) reported that NSE was contained in neurons and in APUD cells. Recently, a large amount of NSE was detected in APUDomas (Tapia et al. 1981), and its content in serum was found to be well correlated with the rise or the fall of the tumor mass. In the present case, the tumor was suggested to be derived from a neurogenic or APUD cell by the NSE value of the patient serum before histological examination. The serum NSE is considered to be a valuable marker substance for screening and therapeutic monitoring of neuroblastoma and APUDomas (Tapia et al. 1981; Ishiguro et al. 1982). It was also conceivable that NSE was also useful to exclude malignant lymphoma and rhabdomyosarcoma.

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## References

Breathnach AS, Robins (1970) Ultrastructural observations on Merkel cells in human foetal skin (Abstract) J Anat 106:411

Fortman GJ, Winkelman RK (1973) A Merkel cell nuclear inclusion. J Invest Dermatol 61:334–368

Hashimoto K (1972) Fine structure of Merkel cell in human oral mucosa. J Invest Dermatol 58:381–387

Iggo A, Muir AR (1969) The structure and function of a slowly adapting touch corpuscle in hairy skin. J Physiol 200:763–796

Ishiguro Y, Kato K, Shimizu A, Ito T, Nagaya M (1982) High levels of immunoreactive nervous system-specific enolase in sera of patients with neuroblastoma. Clin Chim Acta 121:173–180

Iwasaki H, Mitsui T, Kikuchi M, Imai T, Fukushima K (1981) Neuroendocrine carcinoma (Trabecular carcinoma) of the skin with ectopic ACTH production. Cancer 48:753–756
Mackay B, Luna MA, Butler JJ (1976) Adult neuroblastoma. Electron microscopic observations in nine cases. Cancer 37:1334–1351
McGavran MH (1964) "Chromaffin" cell: electron microscopic identification in the human dermis. Science 145:275
Rosai J (1982) On the nature and nomenclature of a primary small carcinoma of the skin exhibiting endocrine (?Merkel cell) differentiation. Am J Dermatopathol 4:501–505
Rywlin AM (1982) Malignant Merkel cell tumor is a more accurate description than trabecular carcinoma. Am J Dermatopathol 4:513–515
Schmechel D, Marangos PJ, Brightman M (1978) Neurone-specific enolase is a molecular marker for peripheral and central neuroendocrine cells. Nature 276:834–836
Sibley RK, Rosai J, Foucar E, Dehner LP, Bosl G (1980) Neuroendocrine (Merkel cell) carcinoma of the skin. A histologic and ultra-structural study of two cases. Am J Surg Pathol 4:211–221
Sidhu GS (1982) What's in a name? Should it be Merkel cell neoplasm or trabecular carcinoma? Am J Dermatopathol 4:509–511
Stern JB (1982) "Murky cell carcinoma (formerly trabecular carcinoma). Am J Dermatopathol 4:517–519
Takeda A, Matsuyama M, Chihara T, Suchi T, Sato T, Tomoda Y (1982) Ultrastructural and immunohistochemistry of Gastro-Entero-Pancreatic (GEP) endocrine cells in mucinous tumors of the ovary. Acta Pathol Jpn 32:1003–1015
Tang CK, Toker C (1978) Trabecular carcinoma of the skin. An ultrastructural study. Cancer 42:2311–2321
Tapia FJ, Polak JM, Barbosa AJA, Bloom SR, Marangos PJ, Dermody C, Pearse AGE (1981) Neuron-specific enolase is produced by neuroendocrine tumors. Lancet 1:808–811
Toker C (1972) Trabecular carcinoma of the skin. Arch Dermatol 105:107–110
Toker C (1982) Trabecular carcinoma of the skin. A question of title. Am J Dermatopathol 4:497–500
Urmacher C (1982) Trabecular carcinoma is an accurate designation. Am J Dermatopathol 4:507
Winkelmann RK (1977) The Merkel cell system and a comparison between it and the neurosecretory or APUD cell system. J Invest Dermatol 69:41–46
Winkelmann RK, Breathnach AS (1973) The Merkel cell. J Invest Dermatol 60:2–15

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