

A Case of Primary Cutaneous Neuroendocrine Carcinoma

—Merkel Cell Tumor—

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Primary Cutaneous Neuroendocrine Carcinoma (CNEC : or Merkel Cell Tumor) usually occurs as a solitary tumor in middle aged to elderly individuals. This tumor may occur on any layer of the skin but the most frequent location is in the dermis. Electron microscopic studies reveal that the tumor cell contains round, dense core granules similar to epidermal Merkel cell and other cells of the neural crest derived APUD system.

We describe the clinical, histological, electron microscopic, immunohistochemical observation of a case of primary CNEC in a 66-year-old female and discuss the theories regarding the histogenesis of this unusual tumor. (*Ann Dermatol* 3:(2) 153–157, 1991)

Key Words : Primary Cutaneous Neuroendocrine Carcinoma (CNEC)

Primary Cutaneous Neuroendocrine carcinoma (CNEC) is a rare malignant tumor that was first described as trabecular carcinoma of the skin in 1972 by Toker.¹ It has subsequently become more commonly recognized as a distinct entity, as evidenced by the increased frequency of case reports in the literature. On the basis of ultrastructural appearance, the similarity between tumor cells and Merkel cells led to the belief that trabecular carcinoma probably originates from the Merkel cell.^{2,3} Since then, this skin tumor has been known as Merkel cell carcinoma. Most of these tumors are usually located in the dermis and have no histologic evidence of epidermal and appendigeal invasion.⁴ Therefore, there is still much discussion regard-

ing the histogenesis of these tumors, and the entity has been described under a variety of names, including cutaneous APUDoma,⁵ primary small cell carcinoma of the skin⁶, and primary cutaneous neuroendocrine carcinoma.⁷ We report a case of primary CNEC and discuss the origin of this tumor cell.

REPORT OF A CASE

In september 1988, a 66-year-old female presented with one year history of a slowly growing papule on the nose. There was no history of medical illness and she appeared to be healthy. Physical examination revealed a solitary, 1cm sized, dome-shaped erythematous papule on the top of nose (Fig. 1). There were no palpable cervical nodes. Laboratory findings, including complete blood cell count, urinalysis, liver and renal function test were within normal limits. Radiological investigation, including chest and

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skull roentgenogram, UGI series, barium-ene-ma, liver scan, bone scan and abdominal CT re-vealed no abnormal findings. On light micro-scopic examination of the biopsied specimen, the epidermis and upper dermis were intact and tumor mass was located in the lower dermis (Fig. 2). Growth pattern of the tumor consisted of dense nodules and strands of cells separated by fibrous septa. The tumor cell population was generally monomorphic. They had large round to oval basophilic nucleus with finely dispersed granular chromatin and small, inconspicuous nucleolus. Cytoplasm was usually scanty and eosinophilic. Some cells were found in the lumen of the blood vessel. Mitotic figures were not seen(Fig. 3).

An argentaffin staining revealed a negative reaction. In the electron microscope, tumor cells were very uniform in size and shape. Most cells had a large round nucleus with a small cyto-plasmic rim. In the periphery of the cytoplasm, small electron-dense granules were found(Fig. 4). These granules, about 1000A in diameter, were surrounded by a single membrane and contained electron-dense material. The number of granules differed from cell to cell, but all tumor cells had at least a few.

Immunohistochemical staining of paraffin sections with polyclonal antibodies against neuron specific enolase(NSE), chromogranin



Fig. 1. 1cm sized, smooth surfaced erythematous papule on the nose.

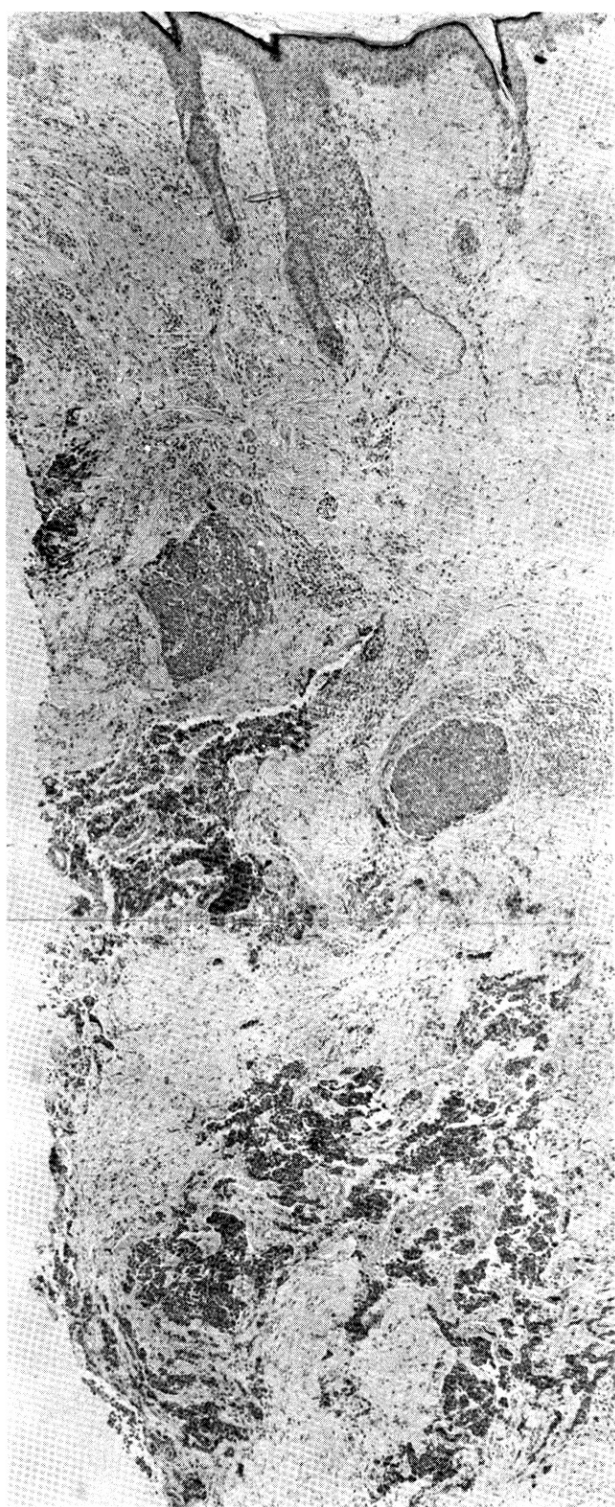


Fig. 2. Irregular tumor masses consisted of nodules and strands are located in the dermis(H & E stain, $\times 40$).

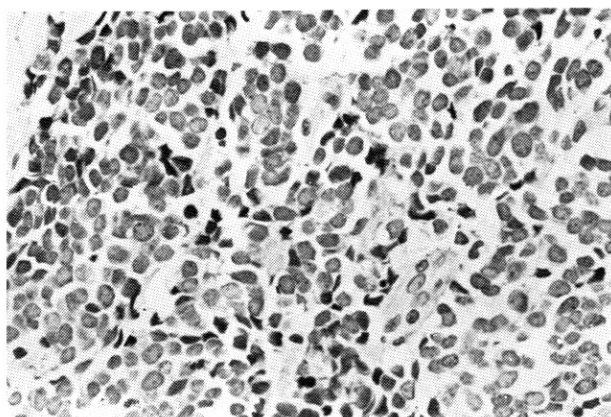


Fig. 3. Individual tumor cells are generally monomorphic and have round to oval nuclei with scanty cytoplasm (H & E stain, $\times 200$).

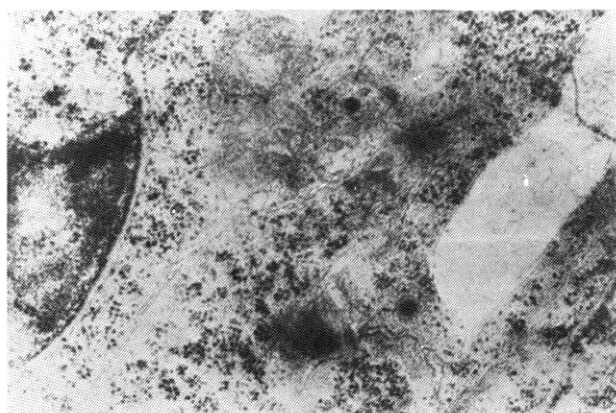


Fig. 4. Electron microscopic findings: small electron dense granules (dia. 1000 Å) surrounded by single membrane (arrow) are found in the periphery of the cytoplasm ($\times 2000$).

and cytokeratin was performed. Staining for NSE was strongly positive in all tumor cells, and positivity for NSE was diffuse in cytoplasm. Staining for chromogranin and cytokeratin was negative. According to these findings, the diagnosis of primary CNEC was made. The patient was treated with surgical excision. The patient had no follow up 5 months after the surgical excision and we were informed of the patient's death by her relative.

DISCUSSION

Primary Cutaneous Neuroendocrine Carcinoma (CNEC) is a highly aggressive tumor which shows a propensity for the sun damaged skin of the elderly.⁸ The tumor presents as a firm raised painless nodule, up to 4.0 cm or more in diameter, which slowly increases in size. The overlying skin may be violaceous, and ulceration is rare. The recurrence rate is 36%,⁴ and metastasis is common. More than 50% of patients have involvement of regional lymph nodes,⁴ and the death rate due to metastatic dissemination exceeds 25%.¹⁰ Histologically, anastomosing cords and strands of neoplastic cells are seen in the dermis and subcutis, but not in epidermis.⁴ The individual cells are monomorphous with round vesicular nuclei and scanty, ill-defined cytoplasm. The granules in the neoplastic cells are argyrophilic. Ultra-structurally the tumor cells are characterized by the presence of paranuclear filament whorls and membrane-bound neurosecretory granules approximately 100–150 nm across. Immunohistochemically the cells of CNEC may be labelled positively with monoclonal antisera to neurofilaments and neuron specific enolase. They may also label positively with antisera to S-100 protein and low molecular weight cytokeratin. More recently, new markers of neuroendocrine differentiation such as chromogranin and synaptophysin have been used to immunostain CNEC.^{11,12,13}

But cytokeratin and chromogranin studies were negative in our case. Because of the small number of neurosecretory granules in CNEC, a negative reaction is possible.¹¹ Although the immunohistochemical and ultrastructural features of tumors indicate neuroendocrine differentiation, and some of these features are shared by Merkel cells, the origin of these tumors remains controversial. Several theories about the origin of this tumor have been sug-

gested : (1) sweat gland epithelium¹ (2) the Merkel cell^{2,3} (3) dermal neuroendocrine cell, not necessarily, Merkel cell^{14,15} (4) cell line of APUD system⁵ (5) pluripotent adnexal stem cell.¹⁶

In 1972, Toker described this tumor as sweat gland carcinoma. But this theory was abated by identification of neuroendocrine granules using the electron microscopy in 1978. Ultrastructural study of these tumors revealed morphologic similarities to normal cutaneous Merkel cells² by the presence of densecore, neurosecretory granules, which led to the belief that this skin tumor is probably of Merkel cell origin. However, the Merkel cell is almost intraepithelial in location, whereas these tumors are almost exclusively dermal tumors without connection to the epidermal epithelia or follicles. These tumors predominate on the head and neck, a distribution that differs from that of Merkel cell. The presence of neurofilament in CNEC, their absence in Merkel cells, and the absence of metenkephalin in CNEC also detract from the theory of an origin from Merkel cell.¹⁶ Dermal neuroendocrine theory was suggested by Merot.^{14,15} Merot^{14,15} observed a dermal neuroendocrine cell which showed all the ultrastructural characteristics previously attributed to the intraepithelial Merkel cell. This cell was located below a pilosebaceous follicle. It is possible that this tumor might be derived from the dermal neuroendocrine cell.

Some authors developed the concept that the tumor cells of CNEC originate from cells belonging to the APUD cell system.^{6,17,18} Carcinoid tumor(APUDoma) arise generally in the bronchus, stomach, small or large bowel and pancreas. Recently there have been cases with the carcinoid tumor appearing in such unusual sites as the kidney, ovary, and thymus. We found four cases in which the carcinoid tumor was a primary tumor of the skin.^{17,18} An atypical carcinoid arising in gastrointestinal or bronchial tract has lymphatic involvement in 10%

to 20% of the cases and usually metastasizes to the liver, brain and bone. Cases of carcinoid with cutaneous metastasis have rarely been reported. They usually have multiple skin lesions over the trunk and on microscopic exam, small gland-like structures are occasionally encountered. An argentaffin staining may be positive.¹⁹

The theory of pluripotent adnexal stem cell origin is based on the similarities between the CNEC and the small cell carcinoma of pulmonary and extrapulmonary origin.^{6,20,21} Ibrahim²¹ thought that Merkel cell carcinoma was primary small cell carcinoma arising in the skin. Morphological and immunohistochemical similarities between CNEC and pulmonary small cell anaplastic carcinoma, which are thought to be of bronchial basal cell origin, suggest that CNEC is also derived from epithelium. Epidemiological, biochemical, and morphological properties of small cell carcinoma are similar to that of CNEC. So, Heenan, et al¹⁶ suggest that neuroendocrine cells of this tumor are likely to be derived from the pluripotent stem cells of epithelium, especially adnexal origin. Recently, this hypothesis represents the best explanation for the origin of the CNEC, as it can also explain some of the particular differentiations observed in the tumor; ie, squamous and glandular differentiation.^{16,22,23}

Our case was characterized by the negative results in all of the laboratory and radiologic findings, particularly of the respiratory and gastrointestinal tract. Because no evidence of the tumor could be found elsewhere in our patient, this seems to be a primary tumor of the skin.

Although the cytokeratin and chromogranin reactions were not compatible with the previous studies in the literature, we considered this case as a primary CNEC according to the consistent findings of the histologic patterns of the tumor, electron dense granules, and strong positive reaction to neuron specific enolase(NSE). The patient had no follow up 5 months after exci-

sion, when we were told of the patients death by her relative.

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