

## Merkel 세포 암종의 압착도말 세포소견 -1예 보고-

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= Abstract =

### Touch Imprint Cytology of Merkel Cell Carcinoma - A Case Report -

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Merkel cell carcinoma (MCC) is a rare primary cutaneous neuroendocrine carcinoma which commonly presents as a skin nodule, and can develop into regional lymph node metastases, as well as spread systematically. Here, we describe the cytological features of a touch imprint of MCC that arose on the face of a 62-year-old female. This touch imprint was acquired from an incisional biopsy specimen which had been submitted for frozen section. The touch preparation produced a highly cellular imprint of loosely cohesive groups of small- to medium-sized malignant cells exhibiting uniform round to oval nuclei, delicate nuclear membranes, fine chromatin, small nucleoli, and scanty cytoplasm, with occasional paranuclear button-like inclusions. We applied cytokeratin 20 to the touch imprint for immunochemistry, allowing us to visualize the tumor cells with paranuclear dot-like positivity. Both the cytological and immunocytological features were quite distinct.

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**Key words:** Merkel cell carcinoma, Imprint, Cytology, Neuroendocrine carcinoma, Skin

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## INTRODUCTION

Merkel cell carcinoma (MCC) of the skin is an aggressive neuroendocrine carcinoma of the skin, which normally presents as a cutaneous nodule, usually in the head and neck or lower extremities of elderly patients.<sup>1-3</sup> The cytology of MCC has been elucidated in several English reports.<sup>4</sup> This neoplasm is a rare tumor, which can resemble small cell undifferentiated carcinoma upon cytological assays. Here, we describe the characteristic features of imprint cytology and immunocytochemistry of MCC, which should prove helpful in the differential diagnosis of malignant small round cell tumor.

## CASE

A 62-year-old female presented with painful swelling over the left malar area of her face. This swelling had persisted for a couple of weeks, and eventually compelled her to visit a regional hospital. The cutaneous lesion measured 2~3 cm, and was characterized by a region of hyperemic skin with an overlying crust (Fig. 1). Under clinical suspicion of cellulitis or a complicated epidermal cyst, appropriate medical treatment was administered, but the patient's symptoms persisted. Chest X-ray and laboratory tests were unremarkable. An incisional biopsy was conducted and the results were submitted for intraoperative consultation. We then prepared touch imprint smears, the results of which were interpreted as malignant small round cell tumor with a list of differential diagnoses, including non-Hodgkin's lymphoma, undifferentiated small cell carcinoma, and rhabdomyosarcoma. Further evaluations were conducted via computerized tomography (CT) of the neck and chest and abdominal ultrasonography, both of which failed to generate any abnormal findings.

### Cytological findings

Touch imprint smears from the tumor were immediately fixed in absolute alcohol, then stained with hematoxylin and eosin. These samples exhibited high

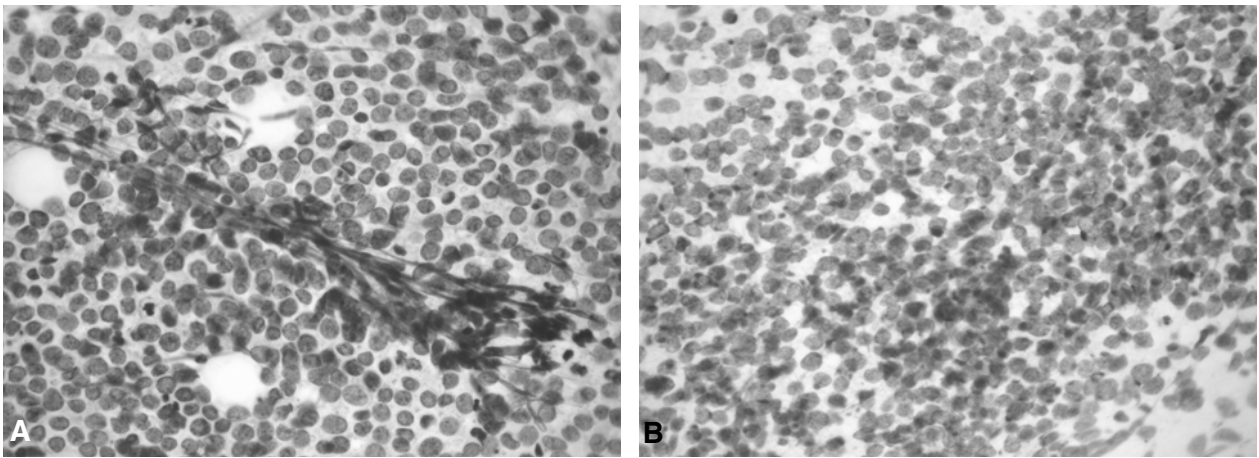


Fig. 1. Skin lesion on the face. The lesion appears an erythematous swelling with overlying crust on the malar area.

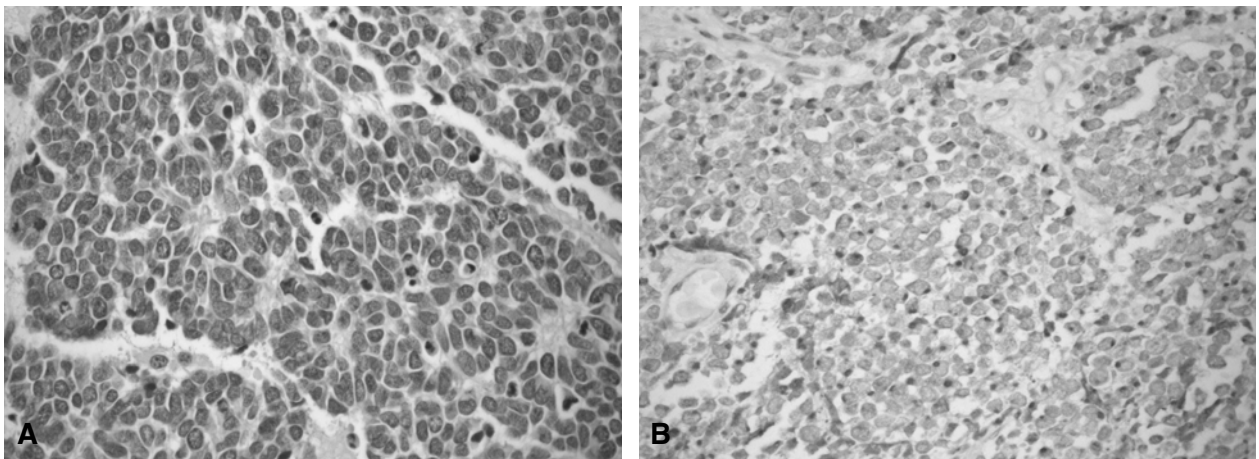
cellularity with a clean background, and revealed sheets and loosely cohesive cell groups of malignant cells, which manifested infrequent mitosis and apoptosis. Although we did note some squeezing artifacts, we detected no sheet-like necrosis. The cellular arrangement within the sheets and the loose cellular groups consisted of small-to medium-sized monomorphic round cells, with a small amount of cytoplasm and occasional cytoplasmic condensation, featuring cytoplasmic caps and paranuclear button-like inclusions (Fig. 2A). We also noted condensations of cytoplasmic material at the core of the rosette-like structures that lacked a fibrillary pattern. Cellular overlapping with regions of nuclear molding was also noted. These features, collectively, appeared to suggest a differential diagnosis of malignant small round cell tumor. The monomorphic tumor cells were somewhat dissociated, resulting in loose clusters of tumor cells with finely dispersed chromatin and small nucleoli, suggesting the possibility of neuroendocrine carcinoma. Immunocytochemistry revealed strong paranuclear dot-like positivity for cytokeratin 20 (Fig. 2B).

### Histopathological findings

The incisional biopsy specimen revealed a pale tan, soft mass with overlying skin. Grossly, the lesion diffusely involved the skin and the underlying soft tissue. The histological section revealed a malignant tumor in



**Fig. 2.** Cytologic and immunocytochemical findings of the touch imprint smear. (A) Smear discloses small to medium sized-monomorphic round cells with finely dispersed chromatin, small nucleoli and occasional cytoplasmic condensation with feature of cytoplasmic caps and paranuclear-dot-like inclusions (H-E). (B) Vague rosette-like configuration without fibrillary pattern and nuclear molding are also seen. Strong paranuclear dot-like positivity for CK 20 is characteristic.



**Fig. 3.** Histologic findings. (A) Histologic section shows solid cords or anastomosing trabeculae of tumor cells with occasional rosette-like configuration. They have monotonous round to oval nuclei with finely dispersed chromatin and small nucleoli. (B) On immunohistochemistry the tumor shows diffuse positivity for neuron specific enolase with paranuclear dot-like accentuation.

the reticular dermis, which was infiltrating the underlying subcutaneous fat and skeletal muscle. Tumor cells were present in the dermis as infiltrating nests, islands, cords, and anastomosing trabeculae of uniform tumor cells, separated by thin and delicate strands of connective tissue delineating the lobules(Fig. 3A). The overlying epidermis and adnexal structure were free of tumor involvement. The individual cells exhibited monotonous round to oval nuclei, featuring finely dispersed chromatin

and small nucleoli. With regard to the immunohistochemical findings, the tumor cells evidenced distinct paranuclear dot-like immunoreactivity for cytokeratin 20. Diffuse positivity for neuron-specific enolase (NSE) with paranuclear dot-like accentuations was also shown to be characteristic(Fig. 3B). These were positive for CD56 and chromogranin, and negative for cytokeratin 7, thyroid transcription factor-1, desmin, CD99, and leukocyte common antigen.

## DISCUSSION

MCC of the skin is a rare primary neuroendocrine carcinoma, which commonly presents as a solitary, firm skin nodule, usually of less than 2 cm in size. Merkel cells, which are routinely detected in the lower epidermis and share features with neuroectodermally-derived cells, are currently thought to give rise to MCC. The most common locations at presentation, in descending order, are in the head and neck region, extremities, and trunks of elderly patients.<sup>1</sup>

A number of published reports in the English literature have detailed the cytomorphological and immunocytochemical features of skin MCC.<sup>3-6</sup> Typically, the aspirates of such patients generate highly cellular smears of loosely clustered and individual, relatively monomorphic, small to medium-sized tumor cells, displaying round to oval, regularly contoured nuclei. Features including a thin cytoplasmic rim, finely granular chromatin, small nucleoli, and occasional nuclear molding within the cell groups have been emphasized. Abundant mitotic figures, occasional rosette-like configurations, and the absence of sheet-like necrosis have also been associated with this condition. In cytological diagnoses of MCC, it is essential to first exclude the possibility of other malignancies that sometimes exhibit a monomorphic small cell pattern. The main differential diagnoses, then, include metastatic small cell carcinoma of the lung, non-Hodgkin's lymphoma, and malignant melanoma.

Unlike pulmonary small cell carcinoma, which is characterized by coarsely granular chromatin and inconspicuous nucleoli, the tumor cells on the imprint smears in the present case exhibited nuclei with finely-dispersed chromatin, delicate nuclear membranes, and small nucleoli. Although the absence of coarse chromatin and the presence of small nucleoli proved helpful in differentiating the present case from metastatic small cell carcinoma, the most peculiar feature of this case was the presence of pale-pink, homogeneous, relatively dense and well-circumscribed round or oval paranuclear buttons. These so-called "perinuclear cytoplasmic caps" or "paranuclear button-like inclusions"

correspond to the intermediate filament buttons, and are thought to account for the perinuclear dot like-pattern of cytokeratin positivity seen in the immunocytochemical results, as well as the occasional strong dot-like positivity for cytokeratin and NSE seen on the immunohistochemical results,<sup>4</sup> which was unusual in the case of metastatic small cell carcinoma. We had the opportunity to apply cytokeratin 20 for immunocytochemistry to the touch imprint smears, which highlighted the tumor cells with paranuclear dot-like positivity. These cytoplasmic caps, which could easily be mistaken for degenerated erythrocytes or so-called lymphoglandular bodies in lymphoproliferative lesions, are considered to be cytoplasmic remnants, which remain partially attached to the nucleus by bundles of intermediate filaments.<sup>7,9,10</sup>

The cytological resemblance of non-Hodgkin's lymphoma to MCC frequently constitutes a diagnostic problem. However, malignant lymphoma is normally seen as a dispersed single-cell population, with lymphoglandular bodies in the background. Lymphoma cells exhibit coarsely-clumped chromatin, usually a single prominent nucleolus, an irregular or folded nuclear membrane, and few mitoses. In the imprint smears of the present case, the tumor cells were arranged in loosely cohesive clusters, and no lymphoglandular bodies were present in the background.

Malignant melanoma usually appears as dispersed pleomorphic cells with abundant cytoplasm, intranuclear pseudoinclusions, and prominent macronucleoli. However, malignant melanoma can also present a variety of other cytomorphological patterns, including an undifferentiated pattern. Immunocytochemistry often provides useful information in differential diagnoses, as malignant melanoma do not exhibit reactivity to cytokeratin.

Other small cell malignancies that must be cytologically differentiated in cytological preparations include rhabdomyosarcoma, primitive neuroectodermal tumors (PNET), metastatic carcinoid tumors, metastatic islet cell tumors, and basal cell carcinoma. Rhabdomyosarcoma usually exhibits frequent bi- and multinucleation, as well as the presence of occasional small cell clusters containing connective-tissue material. The cytological features of a PNET, including rosette formation, may

overlap with those of MCC. However, the imprint smears in the present case revealed no Homer-Wright rosettes with central neuropil. In the histological sections obtained in this case, the tumor cells proved to be negative for CD99. Both metastatic carcinoid tumors and metastatic islet tumors might exhibit cytomorphological and immunocytochemical similarities to MCC. However, these neoplasms normally exhibit at least a moderate amount of readily identifiable cytoplasm, and normally do not exhibit either nuclear molding or significant mitotic activity.<sup>11,12</sup> Basal cell carcinoma is also cytologically reminiscent of MCC. However, basal cell carcinoma usually evidences tightly cohesive groups of small oval cells with hyperchromatic nuclei and characteristic peripheral palisading features.<sup>13,14</sup>

In conclusion, we have described a case of MCC, exhibiting characteristic cytological features on touch preparation. The so-called paranuclear button-like inclusions, which appeared as a paranuclear dot-like pattern on the cytokeratin 20 immunocytochemical tests, appear to be helpful in the cytological diagnosis of MCC.

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