Case Report

# Merkel cell: Friend or felon

Ankita Tandon[1], Narendra N. Singh[1], Nikita Gulati[2]

[1]Department of Oral Pathology, Microbiology and Forensic Odontology, Dental College, RIMS, Ranchi, Jharkhand, [2]Department of Oral Pathology and Microbiology, ITS-CDSR, Muradnagar, Ghaziabad, Uttar Pradesh, India

**Abstract**

Merkel cells are perceived as tactile receptors within skin and oral mucosa containing abundant intermediate filaments but lacking characteristic condensation of tonofilaments, hence are also referred to as non-keratinocytes. Merkel cell carcinomas (MCCs) are primary aggressive neuroendocrine neoplasms occurring in elderly individuals. Toker in 1972 reported MCC of skin pointing towards sweat glands as the source of origin which was later rectified by Tang with the aid of ultrastructural studies as Merkel cells to be a lineage of such tumours. Normally, Merkel cells are abundant in the gingiva and vermillion border of the lip and thus these are the common sites for this neoplasm. Histopathologically, MCC mimics varied other carcinomas, hence requiring a thorough diagnostic protocol. We present a case of challenging histopathology which on immunohistochemical analysis with a unique cytokeratin profile and neurofilament staining pattern helped in reaching a definitive diagnosis.

**Keywords:** Cytokeratin 20, Merkel cell, Merkel cell carcinoma, non-keratinocyte

**Address for correspondence:** Dr. Ankita Tandon, Department of Oral Pathology, Microbiology and Forensic Odontology, Dental College, RIMS, Ranchi, Jharkhand, India.
E-mail: drankitatandon7@gmail.com

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## INTRODUCTION

Human beings enjoy the richness of their tactile environment through touch receptors present in the skin which express mechanically activated ion channels that detect and convert mechanical stimuli into electric signals.[1] Mechanoreceptors are, therefore, specialized receptors that perceive stretch, touch and pressure stimuli through encapsulated nerve endings such as Pacinian corpuscles, Meissner corpuscles and Merkel cells.[2]

First described by Friedrich S. Merkel (1875) as 'Tastzellen' (touch cells) and 'Tastkorperchen' (touch corpuscles) in avian dermis, mammalian epidermis, hair follicles and oral mucosa; Merkel cells are bubble-like cells present within the basal layer of mucosal epithelium[3] and contain characteristic electron-dense granules (80–100 nm)[3] that are located almost exclusively at the side of cytoplasm in contact with axon terminals.[3]

The Merkel cell–neurite complex is thought to be important for mediating gentle touch[1] and in response induces an action potential on the afferent nerve fibres that innervate the cells.[2] These electrical signals are then delivered to the central nervous system, where they are processed and interpreted as touch sensations.[1] Such cells are abundant in areas of skin and oral mucosa involved with sensory perception, such as fingertips, tip of the nose, and palatal rugae.[3]

Speculation suggests that tumours showing differentiation towards this cell type occur in almost all organ types but

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are most common in the gastrointestinal tract followed by the lung. The intra-oral mucosa is among the rarest primary sites where neuroendocrine malignancies specifically involving Merkel cells have been reported.[4]

Recent literature search suggests an upsurge of tumours originating from this system and has therefore drawn attention and intriguing interest towards the origin, nomenclature, etiopathogenesis, histopathology, treatment and prognostic evaluation of such cases. The current case presentation with a review of literature, therefore, aims to focus on the enigmatic behaviour of Merkel cells both in health and in transition to neoplasia.

## CASE PRESENTATION

A 40-year-old male patient presented to a private practitioner with proliferative growth in the lower front tooth region. Growth extended from buccal to lingual gingiva and alveolar mucosa extending from 33 to 46 [Figure 1a]. Extraoral examination revealed enlarged palpable submental lymph nodes. The chest X-ray, bone scintigraphy and ultrasound of the liver showed no abnormalities. Panoramic radiograph showed ill-defined radiolucency from 37 to 46 tooth regions [Figure 1b]. Incisional biopsy revealed sheets of round cell population with cellular atypia suggestive of epithelial malignancy. Mandibular resection and radical neck dissection were performed for the excision of the tumour mass.

### Pathological findings

Excisional specimen revealed varied histopathology, that is, monotonous round small-cell population arranged as sheets and bimorphic spindle and ovoid-shaped cells mostly arranged as clusters, islands and fascicles in a trabecular pattern. Cells had eosinophilic abundant cytoplasm with round or angulated nuclei, prominent nucleoli and

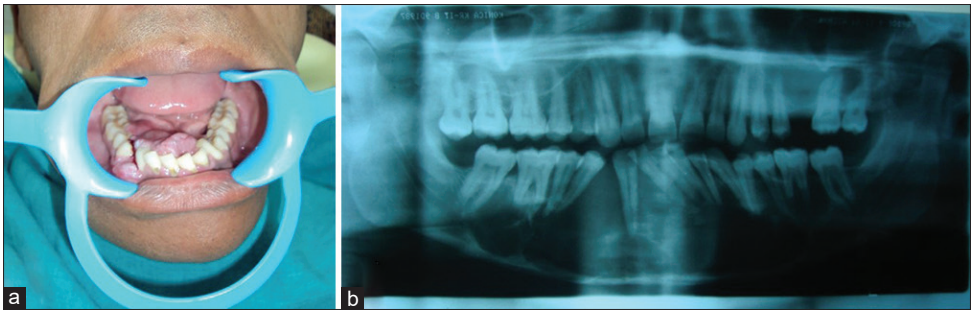


**Figure 1:** (a) Clinical presentation and (b) orthopantomogram

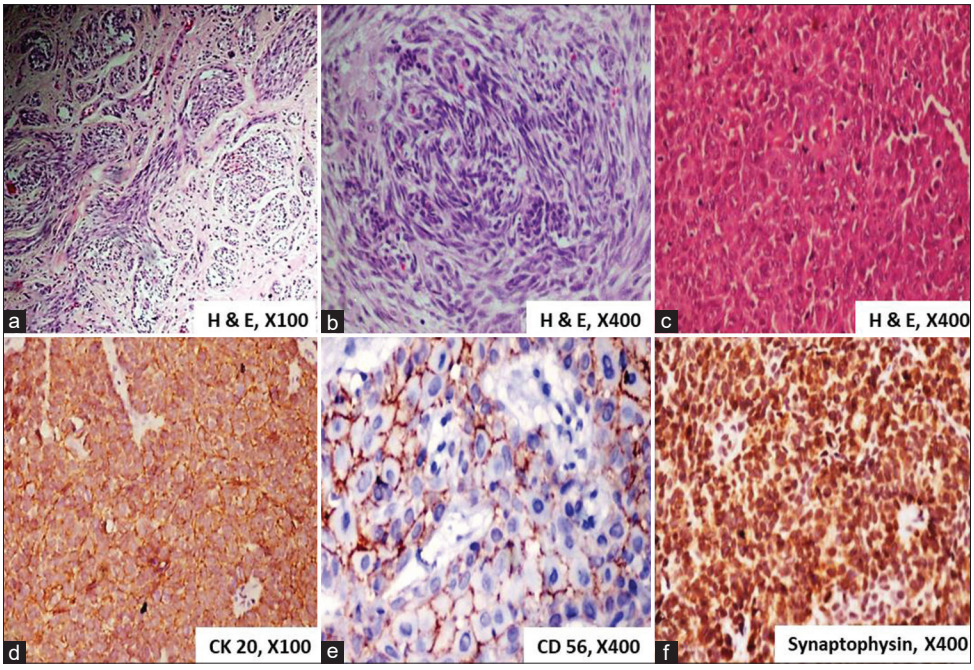


**Figure 2:** (a-c) Histopathology showing small round cells with focal areas showing bimorphic population of tumour cells; (d-f) immunohistochemistry of case using CK-20, CD-56 and synaptophysin, respectively.

**Table 1: Differences between cutaneous and mucosal Merkel cells**

| Cutaneous Merkel cells | Mucosal Merkel cells |
|---|---|
| Arise from epidermal derivatives[12] | Arise from neural crest cells |
| Triangular body with sharpened apex and a flattened base in the basal layer[7] | Round cell body |
| Microvilli are distributed in apical (tightly held by corresponding pits in overlying epithelial cells) and basal (deeply penetrate the basement membrane) aspects of the cell[7] | Microvilli are randomly dispersed along the entire cell surface (some terminate as free nerve endings while others get stuck in adjacent epithelial cells) |
| Possess many secretory granules close to their axon endings[7] | Extend long dendritic paracrine processes to the basal lamina |
| Rodlets absent[12] | Rodlets present |

**Table 2: Summary of previously reported primary Merkel cell malignancies of oral mucosa**

| Author information | Age/ Gender | Chief complaint | Clinical features | Radiographic features | Histopathology | IHC (+/−) | Diagnosis |
|---|---|---|---|---|---|---|---|
| Mir *et al*. (1988)[13] | 53/M | Right jaw swelling | Smooth, lobulated, erythematous, raised lesion that filled and distorted the mucobuccal fold adjacent to the mandibular right second premolar and first and second molar teeth<br>No lymphadenopathy | Radiolucency but no evidence of bone resoption | Submucosal round cell population demonstrating significant mitotic activity. The cells were arranged in sheets and, focally, in a trabecular pattern. Individual cells showed high nuclear-cytoplasmic ratios. A narrow rim of amphophilic cytoplasm surrounded vesicular nuclei containing multiple small nucleoli | +NSE, EMA, synaptophysin, NF, leu-enkephalin | MCC |
| Vigneswaran *et al*. (1992)[14] | 88/M | Fever blister-like lesion on the left corner of his lower lip | Raised, erythematous, ulcerated nodule on the mucosa of the left lower lip<br>H/O Parkinson's disease, osteoarthritis, cataract, and enlarged prostate | | Solid sheets of cohesive, uniformly stained, basaloid, round cells without any significant cellular or nuclear pleomorphism. The tumour cells showed scanty, amphophilic cytoplasm with ill-defined cell boundaries. The nuclei were round to oval, well defined, and exhibited a finely granular chromatin pattern with one or two inconspicuous nucleoli | +CK-8, -18, -19, neurofilament proteins, –NSE, chromogranin A, vimentin, S 100, LCA, B- and T-cell antigens | MCC |
| Inoue *et al*. (1997)[15] | 14/F | Painful swelling in left back tooth region | Left maxillary enlargement from canine to second molar expanding from the buccal to the palatal area measuring approximately 40 mm×40 mm and a movable, reddish mass in the palatal papilla of the first molar<br>No regional or metastatic lymphadenopathy | Highly dense appearance, a so-called sun ray effect like figure. The third molar was pushed up to the auricular region | Tumour composed of small cells of uniform size with basophilic round nuclei. Frequent mitosis with areas of necrosis was evident. The tumour was not well capsulated and invaded deeper tissues with invasion of the palatal bone and erosion of mucous membrane of the maxillary sinus | +NSE and CK-19, CK-13, CK-20, CEA–CD-56, CK-18, vimentin, desmin or neurofilament antibodies | MCC of palatal mucosa |

*Contd...*

**Table 2: Contd...**

| Author information | Age/ Gender | Chief complaint | Clinical features | Radiographic features | Histopathology | IHC (+/−) | Diagnosis |
|---|---|---|---|---|---|---|---|
| Longo *et al*. (1999)[16] | 63/M | Rapidly growing lesion in the floor of mouth | Ulcerated, bleeding nodule in floor of mouth | | The neoplasm composed of medium-sized cells with round and vesicular nuclei demonstrating finely dispersed chromatin positivity granular, dusty, chromatin and prominent nucleoli. Abundant mitotic figures with no evidence of necrosis | +CK, NSE | MCC |
| Yom *et al*. (2006)[17] | 57/M | Swelling on tongue | 2-cm mass in the right lateral dorsum of the posterior tongue anterior to the circumvallate papillae<br>The lesion was raised but without evidence of extension or fixation to adjacent oropharyngeal structures | Radiolucent isolated mass on tongue | Tumour cells were round to polygonal with hyperchromatic nuclei and a scanty rim of amphophilic cytoplasm. Nuclei demonstrated a dense finely granular chromatin in a 'dusty' salt-and-pepper pattern with occasional nuclear moulding and inconspicuous nucleoli | +CK-20, LCA, NSE, chromogranin A, synaptophysin−S-100 | MCC |
| Prabhu *et al*. (2010)[18] | 28/M | Swelling in right lower back jaw | Ulcero-proliferative growth on alveolar mucosa extending from 43–47<br>Submandibular and sublingual lymphadenopathy | Radiolucency from 43 to 47 | Hypercellular tissue composed of spindle and round to ovoid cells arranged in sheets and interlacing fascicles with moderate eosinophilic cytoplasm, round to ovoid nuclei and prominent nucleoli<br>Numerous mitotic figures and areas of necrosis evident | +CK-20, chromogranin−S-100 | MCC |
| Cymerman JA (2013)[19] | 75/M | Painful, non-healing ulcer on the left lateral border of the tongue | 5-mm diameter ulcerated lesion on the left lateral border of the tongue<br>No lymphadenopathy | | Poorly differentiated neuroendocrine carcinoma with a small-cell component | +CD56, chromogranin, synaptophysin, CK20 | NEC |
| Roy *et al*. (2015)[20] | 15/M | Gradually increasing painless swelling | Globular reddish granular mass (4 cm×1.5 cm) in floor of mouth involving lingual frenulum and extending up to right alveolar mucosa along with a base of the tongue<br>Bilateral submandibular, submental and inguinal lymphadenopathy | Radiolucent mass in floor of mouth on CT | Tumour mass composed of trabeculae and nests of tumour cells with high N: C ratio, granular speckled chromatin, scanty to moderate amount of clear vacuolated cytoplasm | +CK-20, CD-56, c-kit, CD-99−p63, TTF-1, CDX2, synaptophysin NSE | MCC |
| de Arruda *et al*. (2021)[21] | 81/M | Painless ulcer | Raised ulcerated nodule of brownish colouration, measuring approximately 20 mm, located at the transition between the skin and the semi-mucosa of the lower lip | – | Sheets and clusters of hyperchromatic small round blue cells that infiltrated the underlying connective tissue and muscle fibres. The nuclei | +pan-cytokeratin (AE1/AE3) and CK-20, chromogranin A and synaptophysin−CD3, CD10, CD20, myeloperoxidase, | MCC |

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**Table 2: Contd...**

| Author information | Age/ Gender | Chief complaint | Clinical features | Radiographic features | Histopathology | IHC (+/−) | Diagnosis |
|---|---|---|---|---|---|---|---|
| | | | | | of tumour cells were pleomorphic, exhibiting salt-and-pepper chromatin | and terminal deoxynucleotide transferase | |

TTF_1=thyroid-transcription factor-1, CK=cytokeratin, NSE=neuron-specific enolase, NF=neuro-filament, CD=cluster of differentiation; MCC=Merkel cell carcinoma, NEC=Neuro-endocrine carcinoma, EMA=epithelial membrane antigen, CA=leukocyte antigen

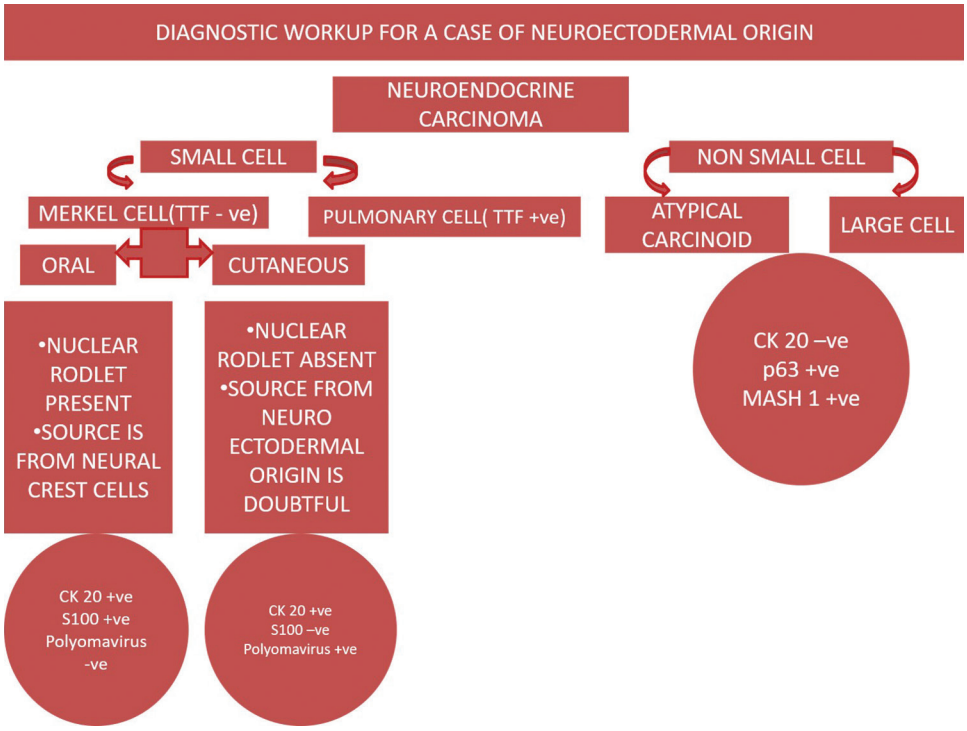


**Figure 3:** Diagnostic workup

granular-speckled chromatin material. Cells revealed pleomorphism with 3–5 mitotic figures per high-power field.

In order to attain a definitive diagnosis, a panel of markers were evaluated in the case. We performed pancytokeratin, S100, vimentin, human melanoma black-45 (HMB-45), thyroid transcription factor-1 (TTF-1) and cluster of differentiation 45 (CD145) leukocyte common antigen (LCA) initially to rule out the lineage of differentiation. Of all, pancytokeratin was positive in tumour cells. Further confirmatory markers such as CK-20, CD-56 and synaptophysin were also positive in the majority of the tumour cell population [Figure 2].

Tumour cells showed positive immunoreactivity for pancytokeratin, CD56, and synaptophysin and negative immunoreactivity for vimentin, LCA, HMB-45 and S100 protein. Taken together, these findings excluded a diagnosis of Ewing sarcoma/primitive neuroectodermal tumour, lymphoma and amelanotic melanoma. Furthermore, a distinctive paranuclear pattern of CK-20 positivity was noted, which is a characteristic feature of MCC together with the expression of the neuroendocrine markers CD56 and synaptophysin. In addition, TTF-1, which is negative in MCC but positive in small-cell carcinoma, was negative in our case. The patient received chemotherapy with etoposide followed by 62 Gy radiation. Follow-up after six months showed remission of the mass and enlarged lymph node.

## DISCUSSION

The origin of Merkel cells is believed to be from the neural crest precursors and hence these are considered to be part of the diffuse neuroendocrine (or amine precursor uptake and decarboxylation) system.[3] This system encompasses a series of cells within which a spectrum of biogenic amines and peptide hormones have been found. Localized aggregations of these cells may constitute certain

endocrine organs such as the adrenal medulla or they may occur as isolated cells scattered throughout all organs with an epithelial lining and are now designated as the disseminated/diffuse neuroendocrine system.[4] Another hypothesis for their origin suggests that these cells originate from certain epithelial cells within the foetal epidermis and that the Merkel cells found in the dermis have detached from the epidermis and migrated to the dermal nerve endings.[5] The second hypothesis is also favoured by the fact that Merkel cells share several ultrastructural features with keratinocytes, such as the occasional presence of 'transitional' cells having tonofibrils (typically located in the perinuclear cytoplasm) and desmosomal attachments to neighbouring keratinocytes (a feature lacking in the neural crest-derived melanocyte).[6] It is also of interest to know that they are always positioned between the direction of the mechanical stimulus and the nerve terminal. Any similar cell without nerve contact may have neuroendocrine, but not mechanoreceptor functions. Such cells have no relationship with the ones originally described by Merkel.[7]

Our case of primary oral Merkel cell carcinoma (MCC) had a histopathological picture mimicking various other lesions such as undifferentiated carcinomas, carcinosarcomas and lymphomas. With the aid of a definitive panel of IHC markers, a conclusive diagnosis of MCC was made.

The varied expression profile of cytokeratins in Merkel cells strongly support the fact that there exists a functionally different Merkel cell subpopulation within the epithelium. Some oral Merkel cells have a stellate appearance due to the presence of thick cytoplasmic processes. These processes consistently contain Merkel cell granules and, as they extend towards both parabasal keratinocytes and the basal lamina, they have been suspected of producing a paracrine secretion affecting keratinocytes and dermal nerve endings. Some Merkel cells contact Langerhans cells with which they communicate via dendrites in which neuropeptides or cytokines are stored.[8-11] Also, the cutaneous and mucosal Merkel cells have distinct properties which are listed in Table 1.

Merkel cells are also known to possess various substances such as adenine nucleotides, neuropeptides, monoamines, chromogranins, synaptophysin and neuron-specific enolase. They also express various cytokeratins including CK-8, -18, -19, and -20. CK-20 is exclusive to Merkel cells within normal squamous epithelium.[8] A thorough literature search regarding primary Merkel cell malignancies within the oral cavity was performed and a summary of such cases has been listed in Table 2.

## CONCLUSION

Merkel cells within oral mucosa are mechanoreceptors. Their transition to neoplasia causing primary oral MCCs is rare. These also pose challenges with both clinical and histopathological diagnosis due to varied and aggressive presentation patterns, thereby influencing the prognostic aspect of the case. Hence, early and correct diagnosis is mandatory to achieve modest therapeutic intervention. Therefore, with the evidence of accumulated data, we have formulated a diagnostic workup, to understand the stride of attaining a tedious diagnosis of MCCs within oral mucosa [Figure 3].

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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### Conflicts of interest

There are no conflicts of interest.

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