CASE REPORT

Merkel Cell Carcinoma of the Buccal Mucosa and Lower Lip

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Abstract Merkel cell carcinoma (MCC) is an uncommon relatively aggressive neuroendocrine dermal neoplasm first described in 1972 as a tumor of the sun exposed skin. Although most MCC affect the skin of the head and neck, rare primarily oral mucosal cases have been documented. Merkel cells are nondendritic neuroendocrine cells that are found not only in the skin but also the oral mucosa and give rise to MCC. Neuroendocrine cells may be found as aggregates in organs or as diffuse or isolated cells within organs and their epithelial lining. They contain peptide hormones and biogenic amines and occur in two forms: dendritic, which are not associated with nerve fibers and non-dendritic, which are associated with nerve fibers. Merkel cells as well as MCC express simple epithelium-type Cytokeratins (8, 18, 19, 20), neurosecretory substances; chromogranin A, synaptophysin, neuron-specific enolase (NSE), adhesion molecules, and villin (intermediate filament). Though weakly, they also express neural markers such as S-100 protein. Cytokeratin 20, and Cluster of differentiation 56, are the two key diagnostic markers for Merkel cells and MCC. Etiology includes UV radiation, the recently described Merkel cell polyomavirus, and long term systemic immunosuppression. The cutaneous and mucosal variants of MCC are considered aggressive tumors with a high risk for local recurrence and metastasis and should be considered in the differential

diagnosis of head and neck mucosal lesions. We present two cases of primary Merkel cell carcinoma, one on the buccal mucosa and the other on the lower lip, and discuss the salient histologic, immunohistochemical and clinical features.

Keywords Merkel cell carcinoma · Dermal neoplasm · Neuroendocrine tumor · Trabecular cell carcinoma

Introduction

The Merkel cell was first described by Friedrich S. Merkel in 1875. Merkel cell carcinoma (MCC), formerly called trabecular carcinoma, was first described by Cyril Toker in 1972 [1, 2]. Merkel cells are nondendritic neuroendocrine cells that are found not only in the skin but also the oral mucosa and give rise to MCC [3]. Toker described it as a trabecular cell carcinoma of the skin after detecting electron-dense neurosecretory granules in the cytoplasm of cells [4, 5]. The name MCC was assigned in 1978 when Chik-Kwun Tang and Cyril Toker found an ultrastructural similarity between these tumor cells and the Merkel cells [1]. Cutaneous MCC, as stated earlier, is a rare and relatively aggressive tumor. Risk factors include UV radiation exposure, Merkel cell polyomavirus, and long term systemic immunosuppression [6]. Less than 2500 cases of this rare skin malignancy have been reported in the last 4 decades. The ratio of melanoma to MCC is about 65–1 among whites, who have the highest incidence overall at 94% of the cases. Patients over 65 years of age are 15 times more likely to be diagnosed with MCC than patients less than 65 years of age. Males are twice as likely to be diagnosed as females.

Immunocompromised patients appear to be at higher risk. MCC has been reported on multiple sites with the most frequent sites being sun-exposed areas of the head and

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neck, extremities, genitals, nasal mucosa, and nasopharynx. Because of its preference for these vulnerable sun-exposed areas of the skin, increasing solar ultraviolet B (UVB) index has been suggested as contributing to the occurrence of MCC. This correlation is further supported by the association of p53 mutations with UVB and the occasional presence of a mutated tumor suppressor gene p53 in MCC. MCC very rarely occurs on mucous membranes of the head and neck

region. In 1988, the first case report of an oral presentation of MCC was published [7]. Reported peri-oral and oral mucosal sites for MCC include the lip, mucobuccal fold, labial mucosa, glossopharyngeal, palatal, tonsillar, floor of mouth, and alveolar mucosa (Table 1). Only 26 cases of perioral and oral MCC have been reported in literature. The progress of the disease is unpredictable and may be wide, ranging from relatively indolent to highly aggressive, often

Table 1 Oral and perioral Merkel cell carcinomas from the English language literature

	Site	Age	Sex	Treatment	Recurrence	Survival rate
1. Toker et al. [8]	Upper lip	76	M	Excision and radiation	Distant metastasis	Not reported
2. Warner et al. [9]	Lower lip	66	M	Not reported	Not reported	Not reported
3. Roenigk et al. [10]	Lower lip	79	M	Surgical excision	Not reported	Not reported
4. Drijkoningen et al. [11]	Lip	80	F	Surgical excision and radiation	Not reported	Not reported
5. Drijkoningen et al. [11]	Lip	74	M	Radiation	Not reported	Not reported
6. Dolezal et al. [12]	Lower lip, midline	62	M	Surgical resection and radiation	Not reported	Not reported
7. Mir et al. [7]	Mandibular buccal fold	53	M	Hemimandibulectomy and regional neck dissection	Unknown	Unknown
8. Boysen et al. [13]	Upper lip	85	M	Surgical excision and neck dissection	Liver metastasis	4 weeks
9. English et al. [14]	Lip	53	M	Not reported	Not reported	Not reported
10. Karam et al. [15]	Lower lip, midline	90	M	Surgical excision	Cardiac	1 year
11. Hayter et al. [16]	Right cheek	73	M	Local excision and radiotherapy	Bone	8 months
12. Vigneswaran et al. [17]	Lower lip, left commissure	88	F	Partial excision and radiation	None	Free of disease at 1 year
13. Inoue et al. [18]	Left hard palate	14	F	Hemimaxillectomy	Local	26 months
14. Longo et al. [19]	Floor of mouth	63	M	Wide resection and radiotherapy	Local	26 months
15. Baker et al. [20]	Floor of mouth, right side	49	M	Surgical resection, right marginal mandibulectomy and right neck dissection	Not reported	10 days
16. Orsini et al. [21]	Lower lip, left side	85	M	Surgical resection and left cervical node dissection	Not reported	3 years and free of disease
17. Hendrix et al. [22]	Right glossopharyngeal fold and base of tongue	56	M	Radiotherapy	Bone	12 months
18. Yom et al. [8]	Right lateral and posterior tongue	57	M	Chemotherapy followed by chemo-radiation	Bone and soft tissue	16 months
19. Yom et al. [8]	Upper lip, midline	89	M	Surgical excision	Nodal	4 months
20. Yom et al. [8]	Lower lip, left side	82	M	Surgical excision and radiation	Nodal	11 months
21. Nagy et al. [22]	Upper lip	79	F	Cryosurgery	None	7 years
22. Nagy et al. [22]	Palatine tonsil	79	F	Partial resection	None	4 months
23. Prabhu et al. [23]	Right posterior mandible	28	M	Right hemimandibulectomy and radiation therapy	None	Alive
24. Roy et al. [24]	Floor of the mouth	15	M	Surgical excision and radiation therapy	None	Alive
25. Current case 1	Right buccal mucosa	76	M	Surgical resection	None	Alive
26. Current case 2	Lower lip, left side	88	F	Surgical excision	None	Alive

with local, regional, and distant spread. Treatment options for oral lesions have not been rigorously evaluated, include surgery alone and/or with adjuvant radiation therapy. Systemic chemotherapy is reserved for recurrent or disseminated disease. We present two cases of this rare and minimally understood entity with one in the oral cavity and the other on the lip.

Case 1

The patient was a 76-year-old previously healthy Caucasian man. Clinically, he sought care due to the presence of a right sided, buccal mass for 2 months. There was no significant past medical history including any neoplasm of the head and neck. Radiographic studies did not show any tumors in the chest or abdominal cavity and no appreciable lymphadenopathy. He underwent surgical excision of the mass. Histologically, the tumor was composed of poorly differentiated cellular proliferation composed of small round blue cells with neuroendocrine features including a “salt and pepper” stippled chromatin pattern. The tumor invaded into soft tissue and attached skeletal muscle with an associated dense mixed lymphoplasmacytic infiltrate. Immunohistochemical (IHC) stains demonstrated that the tumor cells were positive for pan-cytokeratin, synaptophysin, chromogranin and cluster of differentiation (CD) 56 (CD56). The tumor cells exhibited prominent paranuclear dot-like reactivity with Cytokeratin 20 (CK20). Ki-67 labeled almost all tumor cell nuclei. IHC for Thyroid transcription factor-1 (TTF-1), Cytokeratin 7 (CK7) and S-100 were negative. Hematopoietic markers (CD45, CD3, CD20, CD138, Kappa light chain in-situ hybridization (kappa-ISH), Lambda light chain in-situ hybridization (lambda-ISH), Terminal deoxynucleotidyl transferase (TdT) and Myeloperoxidase) were negative. The tumor was classified as a poorly differentiated neuroendocrine carcinoma, consistent with Merkel cell carcinoma. The patient was last reported to be alive and well 8 months after surgical resection. (Clinical photos were not available for this case and due to overlapping staining patterns in both cases only specific diagnostic stains for MCC from case 2 are presented in the manuscript.)

Case Report 2

An 88-year-old Caucasian female presented to the oral and maxillofacial surgeon with a lower left lip swelling of approximately 5 months' duration. Clinical examination revealed a 2.5 cm pink, smooth and firm submucosal mass extending from the left vermillion border into the adjacent soft tissue (Fig. 1a, b). A clinical impression of a salivary duct cyst, mucocele, or lipoma was rendered. The patient had no other significant complain or any pertinent history or finding of any parotid lesions when evaluated clinically.

Fig. 1 **a** Clinical photo exhibiting a 2.5 cm pink, smooth and firm submucosal mass extending from the left vermillion border into the adjacent soft tissue. **b** Post-excision sutured site

Fig. 2 H&E stained tissue shows a malignant epithelial proliferation forming sheets and clusters of hyperchromatic basophilic round cells invading connective tissue stroma (magnification, $\times 200$)

An excisional biopsy was performed and submitted for histopathologic examination. Histopathologic examination revealed a malignant epithelial proliferation arising from ulcerated epidermis (Fig. 2). Deeply hyperchromatic basophilic round cells were seen, invading connective tissue stroma in the form of clusters, islands, and strands. Nuclei of tumor cells exhibited a “salt and pepper” chromatin pattern, significant nuclear hyperchromatism and numerous atypical mitoses (Fig. 3a–c). Foci suspicious for lymphovascular invasion were noted. IHC stains for CK20 (Fig. 4) and neuroendocrine markers, namely, CD56 were strongly reactive with the neoplastic cells (Fig. 5). Immunohistochemistry for Thyroid transcription factor-1 (TTF-1), Cytokeratin 7 (CK7) and S-100 were negative despite adequate controls. A diagnosis of high grade neuroendocrine carcinoma consistent

Fig. 3 H&E stained tissue demonstrates deeply hyperchromatic basophilic round cells invading connective tissue stroma in the form of clusters, islands, and strands. **a** (Magnification, $\times 100$) Nuclei of tumor cells exhibiting a “salt and pepper” chromatin pattern. **b** (Mag-

nification, $\times 200$) Significant nuclear hyperchromatism and pleomorphism is noted. **c** (Magnification, $\times 400$) Higher power view of the same section

Fig. 4 The lesional cells show diffusive membranous immunoreactivity for CK20 (magnification, $\times 400$)

Fig. 5 The neoplastic cells show strong cell membrane immune reactivity for CD56 (magnification, $\times 400$)

with MCC was rendered. No recurrence was noted at the 6 month follow up.

Discussion

Merkel cell carcinoma may arise in the skin as well as perioral and oral tissues. The etiologic factors for cutaneous MCC include UV radiation, long term immunosuppression and Merkel cell polyomavirus (MCV). Though still considered rare, since the past 2 decades the incidence of cutaneous MCC have tripled. This has been attributed to the Merkel cell polyomavirus discovered in 2008 [25]. MCV is present in most MCC tumors and is believed to be contributory to the neoplastic transformation thereby making this discovery a major breakthrough in its diagnosis as well as progression marker. Immunohistochemistry for MCV proteins has enhanced diagnostic tools used to identify MCCs and separate them into MCV-related and MCV-unrelated MCC tumors which in turn may have different etiopathogenesis and prognoses (49). Viral antigens are identifiable in most MCC tumors that facilitates distinguishing MCV-positive MCCs from other tumors [25, 26].

Exact etiologic factors for oral MCC are elusive. Sun exposure as a risk factors for cutaneous MCC do not apply to oral MCCs. Though immunosuppression as well as the use of tobacco and alcohol increases the risk, studies have shown that Merkel cell polyomavirus does not play a major role in oral MCC [26]. Risk factors for lip MCC are like cutaneous MCC. Strict categorization of lip MCC into cutaneous or oral MCC is very difficult. Clinically, perioral and oral MCC usually occurs in older adults. Of the 26 reported cases in literature, 15 are on the lips. Other oral sites included buccal mucosa (3 cases), floor of mouth (3 cases), tongue (2 cases), posterior mandible, palatine tonsil, and hard palate (one case each). A male predilection is noted with 19 cases arising in males. It has varied clinical presentations and may present as a plaque or a nodule giving the appearance of a reactive lesion or a benign or a malignant neoplasm. Clinical differential diagnosis may include a pyogenic granuloma, lipoma, hemangioma, squamous cell carcinoma, lymphoma, or melanoma. Lesions grow rapidly and typically range from 0.5 to 5 cm and may ulcerate in advanced stages. Due to its benign appearance MCC is diagnosed at a later stage. At time of diagnosis most lesions have metastasized to the regional lymph nodes [27]. Approximately 15% of MCCs are diagnosed at metastasis without evidence of a primary and appear to be associated with a better prognosis [28]. A thorough clinical history and radiographic imaging helps distinguish a primary oral MCC from a metastatic lesion to the oral cavity and perioral region.

Histopathologically the tumor is composed of small round to ovoid undifferentiated cells showing intense basophilic

staining, prominent mitosis, and nuclei with dispersed pattern of chromatin and inconspicuous nucleoli. Cells show moderate eosinophilic cytoplasm containing neurosecretory granules. These cells may form trabeculae, sheets and anastomosing trabeculae. The overlying mucosa is intact in most cases and the cells invade the underlying connective tissue frequently involving adjacent fat and muscles. Electron microscopic studies reveals dense-core neurosecretory granules with diameter of 100–250 nm, surrounded by intermediate filaments. IHC staining is a valuable tool for diagnosing MCC. This tumor shows epithelial and neuroendocrine differentiation and exhibits reactivity with CK 20 (perinuclear dot pattern), neuroendocrine markers (chromogranin A, synaptophysin, NSE, and CD56) and neurofilaments. CK20 is sensitive and highly specific marker for MCC [29].

Histopathologic differential diagnosis includes other round blue cell tumors. These may include, Kaposi sarcoma, Ewing sarcoma, lymphoma, rhabdomyosarcoma, primitive neuroectodermal tumor, metastatic neuroblastoma, metastatic small cell carcinoma from lung, and metastatic colorectal or gastrointestinal carcinoma. These entities are separated and discriminated by respective neural, hematologic, neuroendocrine and muscle specific immunohistochemical markers. A diagnostic attempt of distinguishing MCC from small cell lung cancer is challenging based on morphology alone, but can often be accomplished by the presence of CK20 and absence of TTF-1 with immunohistochemical (IHC) staining [30] (Table 2).

MCC has been reported on multiple sites with the most frequent sites being sun-exposed areas of the head and neck. Because of its preference for sun-exposed areas of the skin, increasing solar ultraviolet B (UVB) index has been suggested as contributing to the occurrence of MCC. This correlation is further supported by the association of p53 mutations with UVB and the occasional presence of a mutated tumor suppressor gene p53 in MCC [31]. The association of UVB and p53 mutation is less convincing as an etiology in these sites. The suggestion of a neural crest origin as opposed to an epidermal-keratinocyte cell origin for the Merkel cell might explain the occurrence of this aggressive tumor in sun-protected areas. Although Merkel cells are found primarily in the basal layer of the epidermis they are also present in various anatomical sites including taste buds, eccrine glands, sweat glands, the anal canal and palatine mucosa. No cells have been observed in a state of transition between keratinocytes and Merkel cells. Evidence suggests that Merkel cell precursors migrate from the neural crest into the skin, where they differentiate at that time. This is not a foreign concept, as a similar path is taken by both Schwann cells and melanocyte precursors. A neural crest origin is further supported by molecular studies which have revealed deletions on the short arm of chromosome 1 (1p36) and significant loss of heterozygosity in chromosome 3p21. The

Table 2 Pathologic and immunohistochemical differential diagnosis for Merkel cell carcinoma

Tumor	Positive IHC stains	Negative IHC stains
1. MCC	CK20, chromogranin A, synaptophysin, neurofilament, NSE	Thyroid transcription factor-1, S-100, CK7, Leukocyte Common Antigen
2. Small cell carcinoma of lung	CK7, NSE, TTF-1	CK 20, S-100 protein, LCA Neurofilament
3. Melanoma	S-100	CK 20, CK 7, LCA, TTF-1, neurofilament, NSE
4. Lymphoma	LCA	CK 20, CK 7, NSE, S-100, neurofilament, TTF-1
5. Kaposi sarcoma	Human herpes virus (HHV)-latent nuclear antigen-1 (LNA-1)	CK 20, S-100, NSE, TTF-1
6. Ewing sarcoma/PNET	CD99, FLI-1	CK 20, NSE, neurofilament
7. Primary small cell neuroendocrine carcinoma (SNEC)	Low molecular weight CK, EMA, synaptophysin, chromogranin-A, CD56, CD57	CK 20, S-100, HMB-45, LCA
8. Rhabdomyosarcoma	Myogenin, MyoD, synaptophysin	Cytokeratins, NSE, S-100, LCA
9. Neuroblastoma	Synaptophysin, NB84	Cytokeratins, NSE, S-100, LCA, Myogenin
10. Colorectal or gastrointestinal carcinoma	CK 20, villin	CK 20, villin

1p36 deletion is also common in melanoma and neuroblastoma [32]. Loss of heterozygosity in chromosome 3p21 can also be found in small-cell lung cancer. Overall, there appear to be a number of common genetic changes in MCC and other tumors containing cells of neural crest origin. A mutation in the Merkel cell of neural crest origin offers insight into the occurrence of MCC in non-sun exposed locations.

The distinction between cutaneous MCC and mucosal MCC can be difficult as tumors of cutaneous origin may certainly invade into an adjacent mucosal site. The deep location of the tumor in our case without any evidence of cutaneous involvement suggests a primary mucosal origin. The classic histologic features of intense basophilic staining, prominent mitosis, and nuclei with dispersed pattern of chromatin and inconspicuous nucleoli are all present in this case. Our immunohistochemical staining profile was consistent with MCC and ruled against other tumors included in the differential diagnosis (Table 2).

There is currently no consensus on the appropriate mode of treatment for MCC. Pretreatment evaluations involve the use of a computed tomography (CT) scan or magnetic resonance imaging (MRI) of the chest, abdomen and pelvis to rule out another origin or metastatic site of the tumor. Positron emission tomography (PET) is useful in differentiating MCC from lymph node involvement, or chronic lymphoid leukemia. The use of octreotide scintigraphy, is more common for the staging and treatment of gastrointestinal tumors; however, it may be helpful in the future for diagnosis of MCC. Treatment includes wide surgical resection with negative margins for long term disease-free survival. Sentinel lymph node biopsy is recommended to rule-out lymph node involvement since early lymph node involvement is often detected in MCC. This technique has proven to have less morbidity than lymph node dissection, and seems to be a good predictor of regional lymph node status. In case of

lymph node involvement, lymph node dissection and adjuvant radiotherapy is recommended [33]. The most important prognostic factor for survival and development of distant metastases is the presence of lymph node involvement. Post-operative radiotherapy is recommended in cases of incomplete resection or lymph node involvement. Though post-operative radiation therapy prevents recurrence, it does not increase in overall survival time [34].

Chemotherapy is used in cases of metastatic disease. The more common drug combinations in use, including cyclophosphamide/doxorubicin/vincristine and etoposide/cisplatin have had varied success. Other regimens include other platinum-based compounds and drugs such as prednisone and dacarbazine. No chemotherapy protocol has been shown to consistently improve survival. Ongoing research with interferon, tumor necrosis factor and imatinib may provide some hope for the future. MCC is an aggressive disease with a 3-year survival rate of 50%. Post-treatment patients should be monitored monthly for 6 months and 3 monthly for the next 2 years. Thereafter, the patient should be on a twice a year follow-up protocol.

Conclusion

Mucosal MCC is a rare and aggressive neuroendocrine neoplasm, with a high risk for local recurrence and metastasis, and should be considered in the differential diagnosis of head and neck mucosal lesions. The overall recurrence rate of MCC is 55–79%, most often at the site of the primary lesion or in the lymph node. The median survival for patients with stage I (localized) disease is 26–30 months, stage II (lymph node disease) disease is 18 months, and stage III (metastasis) disease is 5 months. Although the long term prognosis is poor, accurate and early diagnosis combined

with aggressive treatment increases the chance of cure. It is therefore prudent for Oral health care providers, especially oral pathologists and head and neck pathologists to consider Merkel cell carcinoma in the differential diagnoses of oral mucosal and perioral soft tissue neoplasms.

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Compliance with Ethical Standards

Conflict of interest Mohammed N. Islam, Hardeep Chehal, Molly Housley Smith, Sarah Islam and Indraneel Bhattacharyya declares that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants performed by any of the authors.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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