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Clinical and dermoscopic features of combined cutaneous squamous cell carcinoma (SCC)/neuroendocrine [Merkel cell] carcinoma (MCC)

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Abstract

Background—Merkel cell carcinoma (MCC) is a neuroendocrine carcinoma, associated with Merkel cell polyomavirus. MCC admixed with squamous cell carcinoma (SCC) is unassociated with polyomavirus, and is genetically distinct.

Objective—We sought to distinguish clinically and dermoscopically between MCC and SCC/MCC.

Methods—We compared patient data for SCC/MCC (n = 26) and MCC (n = 20), and reviewed clinical and dermoscopic images (n = 9) of SCC/MCC.

Results—Patients with SCC/MCC were older (median 76.5 vs 69 years) and more often male (77% vs 60%), and had more nonmelanoma skin cancer (85% vs 25%), malignant extracutaneous tumors (25% vs 5%), lymphoproliferative disorders (23% vs 10%), and immunodeficient/proinflammatory states (77% vs 35%). In all, 58% of SCC/MCC versus 10% of MCC were clinically diagnosed nonmelanoma skin cancer. Patients with SCC/MCC had more metastases (77% vs 40%), more treatment failures (53% vs 45%), shorter survival (41 vs 54 months), and more death from disease (50% vs 40%). SCC/MCC demonstrated marked scale (7/9), and telangiectasia (1/9). Dermoscopically, small dotted and short linear irregular peripheral vessels and central milky-red areas with large-diameter arborizing vessels were seen.

Limitations—The rarity of SCC/MCC limits available data.

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Conclusions—SCC/MCC is aggressive, arising within elderly patients' chronically ultraviolet-exposed skin, often in the setting of immunosuppression or inflammation. Dermoscopically, polymorphous vessels in lesions suspicious for nonmelanoma skin cancer are suggestive.

Keywords

biphenotypic; dermoscopy; Merkel cell; neuroendocrine carcinoma; polyomavirus; ultraviolet signature

Merkel cell carcinoma (MCC) is a rare cutaneous neuroendocrine carcinoma that typically arises in the background of a clonally integrated virus, the Merkel cell polyomavirus (MCV). MCC has an estimated annual incidence of 0.6 per 100,000 persons. The disease exhibits an aggressive course and there is no definitive cure; mortality for MCC exceeds that of melanoma, with the 5-year disease-specific survival estimated at 30% to 64%.¹ Histologically, MCC co-occurring with non-MCC tumors, particularly squamous cell carcinoma (SCC), comprise 5% to 14% of all MCC.² Combined tumors are increasingly thought to represent a distinct disease process from MCC, with reproducibly absent MCV,²⁻⁴ and a more aggressive course.

We report clinical findings and long-term follow-up data from a series of cutaneous SCC/MCC in comparison with pure MCC. This report highlights the more aggressive nature of combined tumors compared with pure MCC. The clinical examination and dermoscopic findings reported here for SCC/MCC might aid clinicians in identifying this tumor type, potentially reducing delays in diagnosis and appropriate treatment.

METHODS

Patient selection

The study was performed with an approved application for exemption from review by the institutional review board/privacy board of Memorial Sloan Kettering Cancer Center. The pathology department archive was searched for patients with a diagnosis of MCC, with or without the key words "squamous cell." Cases for which slides were available for histopathologic and immunohistochemical confirmation of combined SCC/MCC or pure MCC were reviewed. Specifically, combined tumors showing SCC with a distinct neuroendocrine component (Fig 1) that was typically immunoreactive for CK20 with areas of paranuclear dotlike staining, and/or CAM5.2³ positivity were accepted as SCC/MCC. In these cases thyroid transcription factor-1 and S100 were generally negative, as was the marker for the large T antigen of integrated Merkel cell polyomavirus, CM2B4.³

Clinical data

The main clinical characteristics of patients were retrospectively assessed by patient chart review. Dates of tumor diagnosis and recurrence, along with clinical features, medical history, treatments pursued, and patient outcomes at follow-up were obtained from the patient's medical records.

Clinical and dermoscopic image data

Cases for which only high-quality clinical photographs and dermoscopic images were available were examined. Features assessed included appearance of background skin, lesion size and shape, presence or absence of surface scale, pigment alteration/structures, and presence, quality, and location of vascular structures.

RESULTS

Clinical features of SCC/MCC tumors: photographic review

Clinical features of the tumors from 9 patients with available clinical $\pm$ dermoscopic images are presented in Table I. Six of the 9 tumors presented as firm, dome-shaped, smooth pink to red, sharply demarcated nodules with overlying thick adherent scale (Figs 2 and 3). One such tumor was present as multiple nodules, and another case presented as a papule arising in a surgical scar (Fig 4). Two cases were sufficiently violaceous in color that the clinical suspicion was melanoma (case 5) or hemangioma (case 8). All lesions occurred on sun-exposed sites. The face/scalp was involved in 6 cases, and the neck, back of wrist (Fig 5), and upper aspect of chest (Fig 6) in 1 case each. All patients had significant dermatoheliosis with actinic keratoses, solar lentigines, and telangiectasia in the skin away from the neoplastic growths. Basal cell carcinoma (BCC) (6/9) or SCC (3/9) were the most commonly suspected diagnoses at the time of biopsy. Intraoperative photographs from 2 patients with hyperkeratotic nodules demonstrated well-circumscribed, fleshy dermal nodules deep to and separate from the underlying crust (Figs 2 and 3). Lesions were asymptomatic in all 9 cases.

Dermoscopic features of SCC/MCC tumors

High-quality dermoscopic images were reviewed (Figs 6 and 7). Tumors had surface scale and demonstrated small dotted vessels and short linear irregular vessels at the periphery. In some cases there also were milky-red areas located centrally with large-diameter arborizing vessels. None had white structureless areas, pigment, or a blue-gray veil.

Clinical history, course, and associations of SCC/MCC versus pure MCC

Clinical features of the patients reviewed in this study are shown in Tables I and II. Twenty-six patients, 20 male and 6 female, met inclusion criteria for SCC/MCC. The patients' ages at diagnosis ranged from 50 to 89 (median 76.5) years. Twenty-three patients were Caucasian and 3 patients were of unidentified race/ethnicity. When compared with the group of 20 patients with pure MCC, of the 26 combined SCC/MCC, 58% were clinically diagnosed as BCC or SCC, versus 10% of pure tumors, whereas 45% of pure tumors were thought to be a benign lesion such as a pimple, cyst, dermatofibroma, abscess, or lipoma. Only 15% of combined tumors were thought to be benign, usually vascular lesions, eg, hemangioma. The patients with SCC/MCC were older at the time of diagnosis (76.5 vs 69 years) and were more likely to be male (77% vs 60%). Compared with patients with pure MCC, those with combined SCC/MCC had a greater incidence of nonmelanoma skin cancer (NMSC) (85% vs 25%), lymphoproliferative disorders (23% vs 10%), nonhematologic extracutaneous cancer (25% vs 5%), and other immunodeficient or proinflammatory states

(77% vs 35%) ranging from diabetes mellitus (8/26) to hypothyroidism (3/26), and including viral encephalitis, endocarditis, psoriasis, pleurisy, polio, hepatitis, *Pneumocystis carinii* pneumonia, ulcerative colitis, polymyalgia rheumatica, fungal pneumonia, autoimmune bronchiolitis, chronic steroid use, meningitis, and shingles. Patients with combined SCC/MCC had a higher metastatic rate (77% vs 40%), and the metastases of SCC/MCC typically occurred in the head and neck areas, whereas metastases of pure MCC occurred in both head and neck areas and trunk areas. Patients with SCC/MCC were also shown to have a lower survival (41 vs 54 months average) and more treatment failures (14 vs 9), shown in Table III.

DISCUSSION

SCC is the most common neoplasm to co-occur with MCC, and the frequency of this association is higher than chance.⁵⁻⁷ Reported incidences of concurrent MCC and SCC range from 5% to 34%.^{2,8} Molecular and immunohistochemical analyses suggest 2 modes of MCC tumorigenesis: MCV-dependent and MCV-independent. The MCV-independent pathway gives rise to tumors marked by ultraviolet (UV)-associated aberrant p53 expression.^{9,10}

Combined SCC/MCC are often negative for integrated MCV,^{3,4,7,11-13} and all of our combined SCC/MCC tumors were MCV negative by immunohistochemistry and polymerase chain reaction.³ Recently we showed that combined SCC/MCC have a distinct UV-associated mutational profile, different from pure MCC.¹⁴ The current study lends further support for UV association in combined tumors, as all cases clinically arose in a background of extensive actinic damage.

The association of MCC with SCC in combined tumors may be indicative of an immunosuppressive state. Patients with chronic lymphocytic leukemia and non-Hodgkin lymphoma have an increased incidence of NMSC and higher recurrence rates after surgery. Immunosuppression is associated with poorer SCC prognosis, and is considered to play a role in MCC. Our study shows that compared with patients with pure MCC, those with combined SCC/MCC had a greater incidence of lymphoproliferative disorders, nonhematologic extracutaneous cancer, and other immunodeficient states.

MCC behaves aggressively, with 5-year survival of 75%, 59%, and 25% for primary tumors, lymph node metastasis and/or local recurrences, and distant metastasis, respectively. Prognosis is poor and is most influenced by the presence or absence of lymph node metastasis and lymphovascular invasion.^{1,15} In contrast, the overall prognosis of cutaneous SCC is excellent, with an overall 5-year cure rate of greater than 90% and an estimated yearly disease-specific mortality of 1% to 4%.¹⁶⁻¹⁹

At our institution approximately 4000 cases of cutaneous pure SCC are diagnosed per year, whereas cases of combined SCC/MCC are quite rare. We note differences in survival from diagnosis, and the more frequent occurrence of both metastasis and death in SCC/MCC (13/26 dead and 20/26 with metastasis with 22-month median follow-up) versus pure MCC (8/20 dead and 8/20 with metastasis with 46-month median follow-up). Given the rarity of

these tumor subsets and the scant available long-term follow-up data in these patients, our study is small, not stage-controlled, and insufficiently powered to determine statistical significance. Our institution is a referral center for high-risk skin cancers, which might explain why there are more cases of combined tumors than pure MCC available for review in our database.

The high incidence of lymph node involvement at the time of diagnosis might reflect diagnostic delays, as MCC is frequently mistaken clinically for a benign lesion.²⁰ In this series, the clinical diagnosis of MCC was never a consideration. Given that the neuroendocrine component of these tumors often occurs in the dermis, biopsy specimen that is too superficial could miss the diagnostic material, contributing to delays in diagnosis and initiation of adequate treatment.

Dermoscopy may alert clinicians to biopsy presumed NMSC with atypical or polymorphous vascular patterns. Reported dermoscopic features of MCC include homogenous pink tumors with polymorphous vascular patterns.^{21–25} Milky-red areas/globules, polymorphous vessels, and linear-irregular vessels are the commonly identified vascular patterns.²⁵ The presence of arborizing vessels or glomerular vessels can mimic BCC and Bowen disease, respectively. In the current series, the constellation of a polymorphous vascular pattern with milky-red areas/globules, with marked scale-crust, in a chronically UV-exposed location, engenders prioritizing that site for biopsy. A limitation of our study is that high-quality dermoscopic images were not available for all cases. With dermoscopy becoming more widely used in clinical practice, future studies will benefit from more comprehensive photographic cataloguing of these lesions.

In summary, SCC/MCC arose on actinically damaged skin of elderly Caucasian adults with a history of multiple NMSC. These tumors were often biopsied because of a suspicion for SCC, BCC, or a vascular tumor, but never to rule out MCC. Review of the corresponding dermoscopy suggests that the presence of polymorphous vessels and milky-red areas/globules in a tumor that clinically appears to be SCC or BCC can alert the clinician to the possibility of these aggressive tumors. Given that the MCC component frequently exists within the dermis, and not in the epidermis, biopsies inclusive of dermis should be performed when evaluating potential NMSC, so as not to miss an underlying deadly neuroendocrine component with a too superficial shave, causing delays in diagnosis and treatment of this aggressive and often fatal tumor.

Abbreviations used

BCC	basal cell carcinoma
MCC	Merkel cell carcinoma
MCV	Merkel cell polyoma virus
NMSC	nonmelanoma skin cancer
SCC	squamous cell carcinoma

UV ultraviolet

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Fig 1.

Combined squamous/Merkel cell carcinoma. At low power, the biopsy specimen of the tumor from case 2 shows 2 distinct cell populations. The boundary of the tumors is distinct, the squamous component consisting of atypical pleomorphic keratinizing cells with squamous eddies (*right arrow*) and the neuroendocrine component consisting of a smaller round blue cell proliferation in the dermis (*left arrow*). (Hematoxylin-eosin stain; original magnification: $\times 40$.)

Fig 2. Combined squamous/Merkel cell carcinoma, case 1. Scale-crusting nodule on the right temple (A). Intraoperative finding of a smooth, hard, erythematous subcutaneous nodule (arrow) (B).

Fig 3.

Combined squamous/Merkel cell carcinoma, case 3. Erythematous nodule on the left temple with adherent yellow scale-crust (**A**). Intraoperative close-up examination, after scale-crust removed by curettage, reveals a smooth firm erythematous nodule (*arrow*) (**B**).

Fig 4. Combined squamous/Merkel cell carcinoma, case 2. An erythematous papule within a scar from prior basal cell carcinoma excision.

Fig 5. Combined squamous/Merkel cell carcinoma, case 4. An erythematous scaling nodule on the back of left wrist. Background dermatoheliosis with prominent telangiectasia, atrophy, and wrinkling, along with scattered solar lentigines.

Fig 6.

Combined squamous/Merkel cell carcinoma, case 5. **A**, Erythematous nodule on the upper aspect of chest with adherent scale; background dermatoheliosis with atrophy and wrinkling, along with a nearby actinic keratosis (upper left corner). **B**, Dermoscopy with milky red areas centrally (*small top arrow*) and large-diameter arborizing vessels at the periphery (*larger lower arrows*).

Fig 7. Combined squamous/Merkel cell carcinoma. Dermoscopy from case 2 with central scale (*large left arrow*) and small dotted vessels at periphery (*small arrows*). Short linear irregular vessels are at the superior, right, and lateral aspect of the tumor (*large top right arrow*).

Table I

Clinical characteristics of combined squamous and Merkel cell carcinoma

Case	Age, y/Sex	Location (primary)	Clinical impression	Metastasis	Past skin cancers	Other malignancies	Immune disease
1*	67/M	R preauricular	SCC	Y	BCC, SCC	CLL	N
2*	76/F	L temple	BCC	Y	BCC, SCC		N
3*	79/M	L temple	BCC	Y	SCC	Monoclonal gammopathy	Y
4*	74/F	L back of forearm	BCC vs SCC	Y	BCC, SCC, MIS		Y
5*	82/M	R chest	Melanoma	N	SCC		N
6*	77/M	R lower cheek	BCC vs SCC	N	SCC		N
7*	70/M	L frontal scalp	BCC	Y	SCC	DLBCL	N
8*	84/F	R neck	Angioma	Y	SCC	CLL	N
9*	50/M	R forehead	BCC	Y	BCC, SCC		Y
10	66/M	L scalp	Red mass	Y	MCC	Metastatic colon cancer	Y
11	65/M	L ear	SCC	N		CLL	Y
12	65/M	R front of scalp	Bleeding lesion	Y	BCC, SCC		Y
13	52/M	L side of thigh	Lesion	Y	BCC, SCC	CLL	Y
14	72/F	L temple	Brown palpable lesion	Y	BCC	Breast cancer, ovarian cancer, Waldenstrom macroglobulinemia	N
15	78/M	L calf	Lump	N	BCC, SCC		N
16	82/M	Mid upper forehead	Angioma vs BCC	Y	SCC		Y
17	78/M	L inguinal node	Red plaque	Y	SCC		Y
18	82/M	L scalp	SCC	Y	SCC	Lung carcinoma, Larynx SCC	Y
19	87/M	Scalp		Y		Lipomatous tumor L thigh, prostate cancer, high-grade myxoid fibrosarcoma R thigh	N
20	84/M	R scalp	BCC	Y	BCC, SCC		Y
21	84/M	L forehead	BCC	Y	SCC		Y
22	55/M	Mid scalp	AK rule out SCC	Y	SCC		Y
23	82/F	R side of neck	BCC	Y	SCC		Y
24	64/F	L clavicle	PG vs melanoma	Y			Y
25	89/M	R chest	Bump, BCC	N	Melanoma		N
26	74/M	L back of forearm	Pimple	N	BCC, SCC	High-grade squamous/glandular parotid tumor	N

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AK: Actinic keratosis; *BCC*: basal cell carcinoma; *CLL*: chronic lymphocytic leukemia; *DLBCL*: diffuse large B-cell lymphoma; *F*: female; *L*: left; *M*: male; *MCC*: Merkel cell carcinoma; *MIS*: melanoma in situ; *N*: no; *PG*: pyogenic granuloma; *R*: right; *SCC*: squamous cell carcinoma; *Y*: yes.

* Cases with photographic images available for review.

Table II

Clinical characteristics of pure Merkel cell carcinoma

Case	Age, y/Sex	Location (primary)	Clinical impression	Metastasis	Past skin cancers	Other malignancies	Immune disease
1	68/M	L back of arm	Unspecified	Y	BCC		Y
2	56/M	L upper arm	Unknown	Y			N
3	82/M	L axilla	Unknown	Y			N
4	64/F	L buttock	Abscess	N			Y
5	62/F	L forearm	Lump	Y			N
6	32/F	L ear	CNH vs pyoderma	N			N
7	70/F	L buttock	DF vs sarcoma	N			N
8	58/M	L arm	BCC, lipoma	N			Y
9	51/M	Mid neck	KA	Y	SCC		N
10	74/M	L thigh	B-cell lymphoma	N	Melanoma	CLL	N
11	85/F	R upper cheek	Cyst, pimple	N	BCC, SCC	Low-grade lymphoma	N
12	69/M	L scalp	Lesion	N			N
13	79/F	L cheek	Sarcoma	N			N
14	72/M	L frontal scalp	Unknown		MIS		N
15	73/F	L cheek	Cyst	Y			Y
16	41/M	L calf	Bleeding lesion	N		Prostate carcinoma	N
17	71/M	L cheek, postauricular	Pimple	Y	BCC, SCC	Colon cancer, pharyngeal cancer	Y
18	75/M	R thigh, R chest	Pimple	Y			Y
19	45/M	L buttock	Traumatic nodule	Y			Y
20	59/F	L cheek	Mass	N			N

BCC, Basal cell carcinoma; CLL, chronic lymphocytic leukemia; CNH, chondrodermatitis nodularis helioides; DF, dermatofibroma; F, female; KA, keratoacanthoma; L, left; M, male; MIS, melanoma in situ; N, no; R, right; SCC, squamous cell carcinoma; Y, yes.

Table III

Long-term clinical follow-up summary

	Combined SCC/MCC	Pure MCC
Sex, M:F	20:6	12:8
Age, y (at diagnosis)	73 (median 76.5)	64 (median 69)
Death in follow-up	13/26 (50%)	8/20 (40%)
Survival, mo	41 (median 22, range 3–173)	53.5 (median 46, range 17–153)
Metastases	20/26 (77%)	8/20 (40%)
Site of tumor	18 head/neck, 5 limb, 3 trunk	9 head/neck, 9 limb/1 buttock/1 axilla
LPD	6/26 (24%)	2/20 (10%)
Treatment failures	13 (4 twice, 1 thrice)	9 (3 twice, 1 6 times)

F, Female; *LPD*, lymphoproliferative disorder; *M*, male; *MCC*, Merkel cell carcinoma; *SCC*, squamous cell carcinoma.