# 84-year-old woman with a right cheek mass

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## CLINICAL PRESENTATION

An 84-year-old female patient was referred to a local oral and maxillofacial surgeon for evaluation of an enlarging right cheek mass of 3 months' duration. The lesion was first noted by the treating dentist after restorative procedures performed in the right upper quadrant. Proximity of the lesion to the site of prior maxillary buccal infiltrations led to an initial clinical impression of a hematoma secondary to local anesthetic injection. The patient's medical history was noncontributory. Extraoral examination revealed a firm, nontender, subcutaneous lesion of the right cheek measuring 4.2 (lateral-medial) × 3.5 (superior-inferior) × 2.0 (anterior-posterior) centimeters (cm) (Fig. 1). The overlying skin surface had patchy erythema with focal telangiectasia. Intraorally the mass lesion could be palpated through the buccal mucosa; however, no change in the color or appearance of the buccal mucosa was identified. The remainder of the intraoral examination was unremarkable. An axial bone-window contrast-enhanced computed tomography scan of the face at maxillary level indicated a well-defined, nonenhancing mass of muscle-like attenuation localized in the subcutaneous tissue of the right midface (Fig. 2).

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis for an indurated, erythematous subcutaneous facial lesion can be broadly divided into 3 categories: neoplastic, autoimmune/inflammatory, and infectious. Neoplastic causes considered as part of the differential included angiosarcoma (AS), Kaposi sarcoma, Merkel cell carcinoma, and lymphoma. Possible autoimmune and inflammatory conditions included were granulomatosis with polyangiitis (formerly known as Wegner granulomatosis), sarcoidosis, and cutaneous lupus erythematosus. Infectious entities in our differential were extrapulmonary tuberculosis and tertiary syphilis.

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Although head and neck sarcomas are generally rare, accounting for only 1%−2% of head and neck neoplasms, AS specifically has a predilection for this site.[1] ASs are malignant vascular neoplasms that recapitulate the features of normal endothelium. This entity is subdivided into 5 clinical categories, including primary cutaneous, postirradiation, lymphedema associated, AS of deep soft tissue, and AS of parenchymal origin. Of the cases of primary cutaneous AS, more than 50% occur in the head and neck region. Cutaneous AS predominantly occurs in older adults, with a propensity for the scalp. It tends to present initially as a red to purple bruise-like lesion or nodule that may be mistaken for a benign entity and lead to delayed diagnosis. If untreated, the lesion will continue to grow, leading to extensive local spread and surface ulceration.[2] Both the clinical appearance of the lesion and our patient's demographic information were consistent with an AS, and for these reasons this entity was strongly considered in our differential diagnosis. Our patient did lack other known risk factors for AS, including previous radiation, chronic lymphedema, and exposure to vinyl chloride.

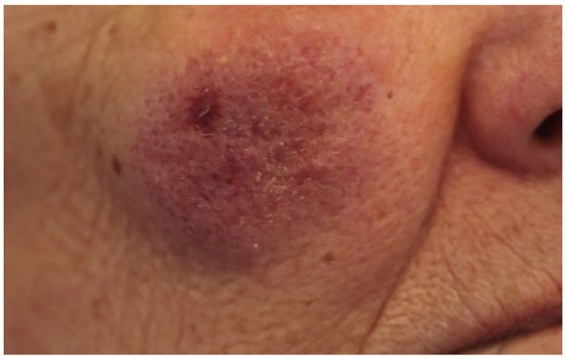

Fig. 1. Firm, nontender, subcutaneous lesion of the right cheek. The overlying skin shows patchy erythema with focal telangiectasia.

Merkel cell carcinoma (MCC), also known as neuroendocrine carcinoma of the skin, is a rare aggressive tumor that presents most often in the head and neck region of elderly individuals. The salient clinical features of MCC are commonly summarized by the acronym AEIOU: *a*symptomatic, *e*xpanding rapidly, *i*mmune suppression, *o*lder than 50 years of age, and *u*ltraviolet (UV)−exposed site.[3] Two distinct causes have been proposed for this lesion: infection with Merkel cell polyomavirus (MCPyV), which was first

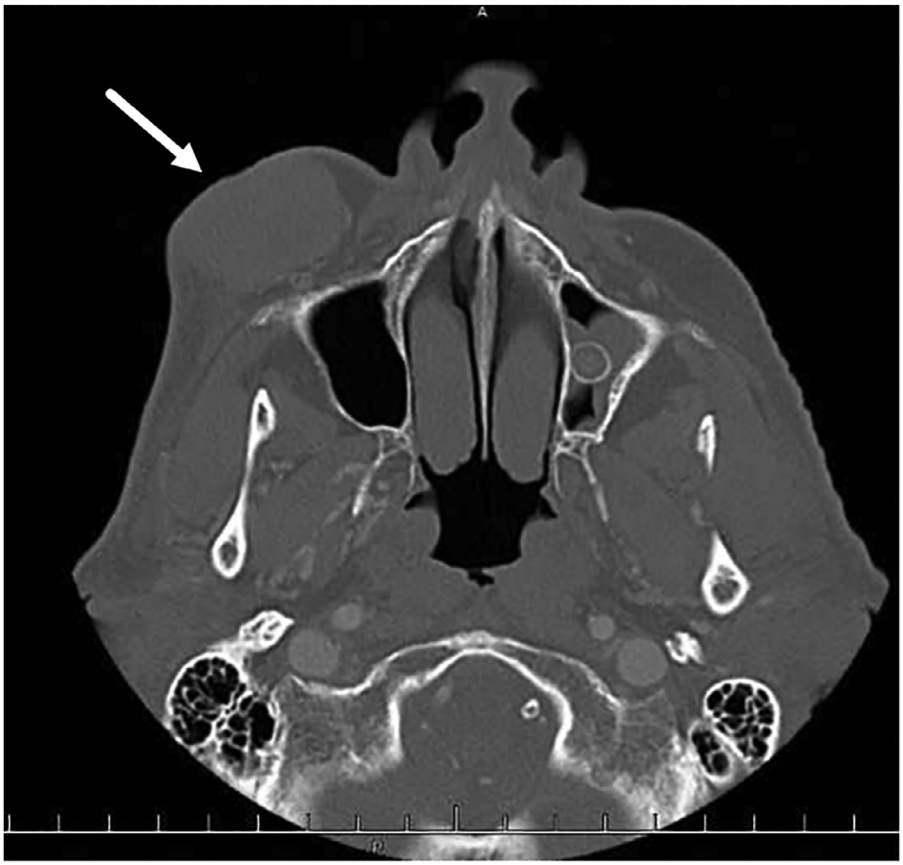

Fig. 2. A computed tomography scan of the face at maxillary level shows a well-defined, nonenhancing mass of muscle-like attenuation localized in the subcutaneous tissue of the right midface (indicated by arrow).

identified in 2008 and has been documented in approximately 80% of cases of MCC, and accumulation of UV-induced mutations.[4] Our patient matched 4 out of the 5 AEIOU descriptors and for these reasons MCC was considered high on our differential diagnosis.

Kaposi sarcoma (KS) is a multifocal mucocutaneous neoplasm of endothelial origin first described by Moritz Kaposi in 1872. The disease has 4 major clinical forms: classic or Mediterranean KS, acquired immunodeficiency syndrome (AIDS)−associated KS, iatrogenic or post-transplant KS, and African (endemic) KS. The causative agent implicated in all forms is human herpesvirus 8, also known as Kaposi sarcoma−associated herpesvirus. Clinically, KS can present as macular, nodular, raised, or ulcerated lesions that range in color from red to purple. Early lesions tend to be red, flat, and asymptomatic, whereas more advanced lesions appear darker and are painful.[5] The clinical appearance of our patient's lesion was consistent with KS; however, a lack of associated risk factors in her history made this diagnosis unlikely.

Lymphoma is broadly defined as a malignancy of the lymphatic system and subclassified as either Hodgkin lymphoma or non-Hodgkin lymphoma, each of which is then divided into specific subtypes. Although the majority of lymphomas in the United States originate in lymph nodes, some may spread to involve or primarily affect the skin. The most common type of cutaneous lymphoma is a malignancy of CD4 T cells known as mycosis fungoides. When the skin is affected, patients may present with patches, plaques, or tumors, which can vary in color and texture. Although the clinical appearance of the lesion in our patient may be consistent with that of a cutaneous lymphoma, the lack of multifocality would be unlikely for a condition such as mycosis fungoides, which simultaneously involves multiple body sites.[6] For this reason, lymphoma was given lower consideration on our clinical differential diagnosis.

Granulomatosis with polyangiitis (GPA), formerly termed Wegener granulomatosis, is an autoimmune process that presents with granulomatous inflammation and systemic vasculitis. The cause is unknown; however, lesions may develop after a minor traumatic event. GPA can be classified as generalized when it involves both the respiratory and renal systems, limited when there is only respiratory involvement, and superficial when restricted to the skin and subcutaneous tissues. Cutaneous lesions have had a site predilection for the trunk and extremities; however, any cutaneous site

may be involved. The most common clinical presentation of cutaneous lesions is palpable purpura, although the appearance of cutaneous GPA varies widely and can include erythema nodosum−like nodules and ulcers.[7] Intraoral manifestations of GPA can also vary, but patients may classically present with ulcers and/or friable and hemorrhagic gingival lesions known as strawberry gingivitis. The American College of Rheumatology has established a set of diagnostic criteria for GPA, which include the presence of oral ulceration or nasal discharge, nodules or cavities on chest images, abnormal urinary sediment, and granulomatous inflammation in biopsy specimens. At least 2 of these features are required for a diagnosis of GPA. Additionally, the identification of Proteinase 3/Cytoplasmic Antineutrophil Cytoplasmic Antibody (PR3/C-ANCA) serum antibodies is a highly sensitive and specific marker of generalized GPA.[8] Although our patient did not have systemic symptoms consistent with GPA, cutaneous lesions may represent the first clinical sign of this condition, and for this reason GPA could not be definitively excluded from the differential.

Sarcoidosis is defined as a chronic granulomatous disease of unknown causes. It has a slight female predilection and usually presents before the age of 40 years. Clinical signs initially may include pulmonary, eye, or skin manifestations, with head and neck involvement occurring in 10%−15% of patients.[9] Cutaneous manifestations of the head and neck region have variable clinical presentations known to mimic many different lesions, which has led to sarcoidosis being termed the great imitator. Skin lesions of sarcoidosis include subcutaneous nodules, plaques, and indurations of previously scarred skin, as well as a red-purple indurated plaque-like and nodular fibrotic skin lesion, which is referred to as lupus pernio.[10] These cutaneous manifestations can occur late in disease or can be an initial finding. The lesion in our patient clinically resembled lupus pernio and could have represented the first clinical manifestation of sarcoidosis given she had no known history of this condition. Considering her age and lack of other pertinent clinical and radiographic findings, this would be exceedingly rare but could not be fully discounted. For this reason sarcoidosis was included on the differential diagnosis but was given low consideration.

Cutaneous lupus erythematosus (CLE) is an autoimmune condition with a highly variable clinical presentation. CLE is broadly divided into 3 categories: acute CLE, subacute CLE, and chronic CLE. Within each of these categories, the disease is further categorized into additional subtypes. Of interest to our case is discoid lupus erythematosus (DLE), a subtype of chronic CLE. DLE often presents in the head and neck region, without other evidence of systemic disease, and is often seen in women in the fourth and fifth decades of life. Early lesions of DLE present as well-demarcated, indurated, and erythematous macules or papules, which are known to mimic conditions such as sarcoidosis and cutaneous T-cell lymphoma.[11] The rapid expansion of the lesion in our patient, the absence of systemic disease, and her advanced age made CLE a less likely diagnosis, but it could not be excluded from the differential.

Tuberculosis (TB) is a chronic infection caused most often by *Mycobacterium tuberculosis,* although other *Mycobacterium* species may also be implicated. The course of TB begins with an unexposed individual that on exposure develops an initial primary infection, most commonly in the lungs. After this initial infection, which is typically asymptomatic, TB can remain dormant until an inciting event causes reactivation later in life. Reactivation is most commonly seen in a patient with human immunodeficiency virus/AIDS or other immune-compromising conditions. This reactivation is termed secondary TB and has a variety of different clinical presentations. Of interest in this case for inclusion in the differential was a type of cutaneous TB termed lupus vulgaris. This form of TB often presents as multiple skin nodules, which often blanch with pressure (positive diascopy test).[12] Our patient reported no known history of TB infection and presented with a singular nodule negative on diascopy test; therefore TB represents an unlikely diagnosis but could also not be definitively excluded.

Syphilis is caused by infection with the spirochete *Treponema pallidum,* which is most commonly transmitted via sexual contact or congenitally. Syphilis can be divided into 3 distinct stages: primary, secondary, and tertiary. Although development of tertiary syphilis is uncommon, even in untreated patients, those with tertiary syphilis may develop nodular or nodulo-ulcerative granulomatous lesions known as gummas. A gumma clinically presents as a painless, firm, and erythematous nodule deep within the dermis, which then forms a granulomatous ulcer.[13] The early stage of a gumma is consistent with our patient's clinical presentation; however, ulceration was not identified. Additionally, our patient's lack of pertinent medical history or clinical signs and symptoms expected with late-stage syphilitic infection lowered the likelihood of tertiary syphilis on our differential diagnosis.

## DIAGNOSIS AND MANAGEMENT

An incisional biopsy of the lesion was performed transbuccally and submitted for microscopic examination (Fig. 3 A−C). The histologic examination revealed basophilic cells arranged in a trabecular to sheet-like pattern. The neoplastic cells could be seen infiltrating into the dermis and subcutaneous adipose tissue. The individual cells contained granular chromatin, scant cytoplasm, and indistinct cell borders with abnormal mitotic figures and apoptotic nuclei prevalent throughout. These features were suggestive of a tumor of neuroendocrine origin.

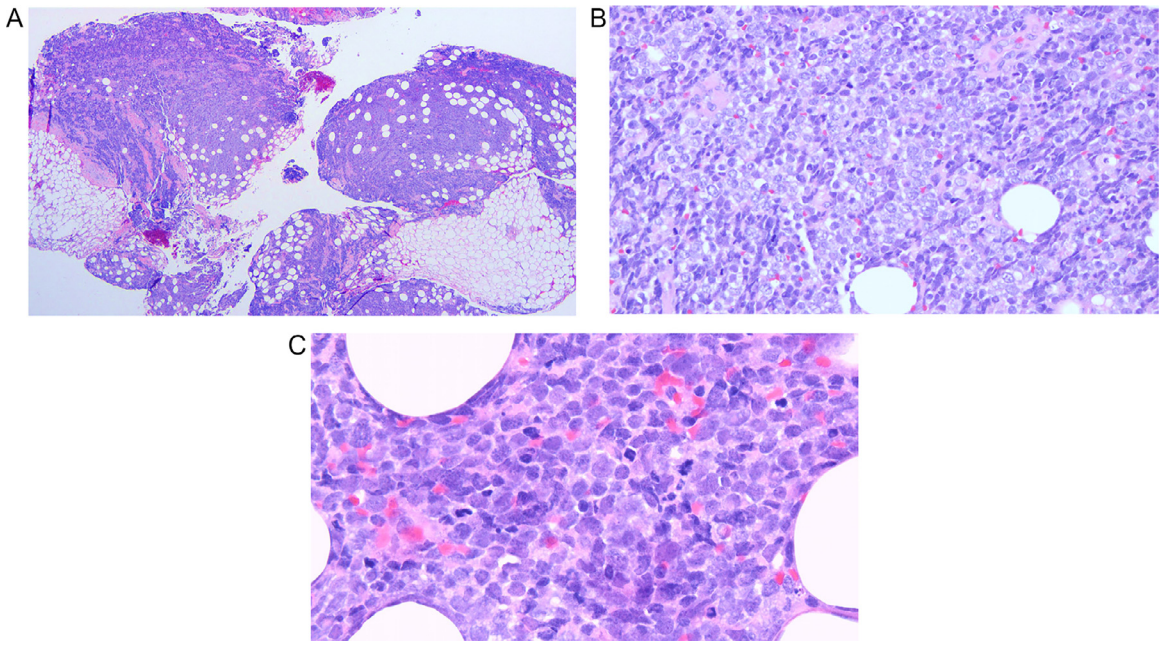


Fig. 3. **(A)** Photomicrograph demonstrating fibrous connective tissue with infiltrating basophilic cell population arranged in a trabecular pattern and with invasion of adjacent adipose tissue, (hematoxylin-eosin [H&E] × 20). **(B)** Hyperchromatic cell population with indistinct cellular borders (H&E × 200). **(C)** Cells show characteristic "salt and pepper" chromatin and there are numerous atypical mitotic figures and apoptotic bodies seen (H&E × 400). A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05647.

Immunohistochemical stains were then used to further classify the lesion (Fig. 4 A–C). The lesional tissue stained strongly positive for synaptophysin and CD56 as well as weakly positive for chromogranin and C-Kit2. Neoplastic cells that stained with CK20 had a perinuclear dot-like pattern, which is characteristic in neoplasms of neuroendocrine origin and can be differentiated from the pattern of CK20 positivity found in metastatic lower gastrointestinal neoplasms. The neoplastic cells were negative for thyroid transcription factor-1 and CK7 (markers positive in small cell carcinoma and medullary thyroid carcinoma); p63 and epithelial membrane antigen (markers positive in neoplasms of epithelial origin); and CD20, CD3, and CD45 (markers with varying positivity in neoplasms of hematologic origin). Subsequent staining with MCPyV indicated positivity in the lesional tissue. Based on both the morphologic features and the immunohistochemical phenotype, a diagnosis of MCC was rendered.

The patient was referred to a major hospital center for definitive treatment. A sentinel lymph node biopsy was performed and found to be positive for MCC. She subsequently underwent wide local excision of the primary site along with elective neck dissection, followed by postoperative radiation therapy. Despite these efforts, the patient died approximately 6 months after the initial diagnosis was rendered due to postoperative complications and disease recurrence.

## DISCUSSION

Merkel cell carcinoma is a rare and aggressive neuroendocrine carcinoma that most commonly occurs on sun-exposed skin of the head and neck in elderly and immunosuppressed patients. It is an aggressive malignancy characterized by frequent recurrence, metastasis, and ultimately a poor prognosis.[14] This lesion was formerly known as trabecular carcinoma and was first described in 1972 by Toker.[15] Although the cause of MCC is not fully understood, proposed causes include UV damage resulting in increased rates of p53 tumor suppressor mutations and infection with a more recently described virus known as Merkel cell polyomavirus. This viral strain has been found in up to 80% of cases and is seen in both primary and metastatic disease.[16] The prevalence of coinfection with MCPyV in MCC has led to the suspicion that the virus may be oncogenic; however, the role of MCPyV in tumorigenesis is not fully understood. The incidence rate of MCC has tripled from 1986 to 2001, a trend that has been speculated to result from either the spread of MCPyV or an increase in the solar ultraviolet B index.[17]

MCC occurs most commonly in elderly patients in the sixth to seventh decades of life, although rare cases have been reported in patients as young as 14 years old.[4,18] This lesion has a male predilection of approximately 1.6:1 and predominantly affects Caucasians, with one review of 3870 cases finding a 94.9% frequency. Risk factors for MCC include sun exposure,

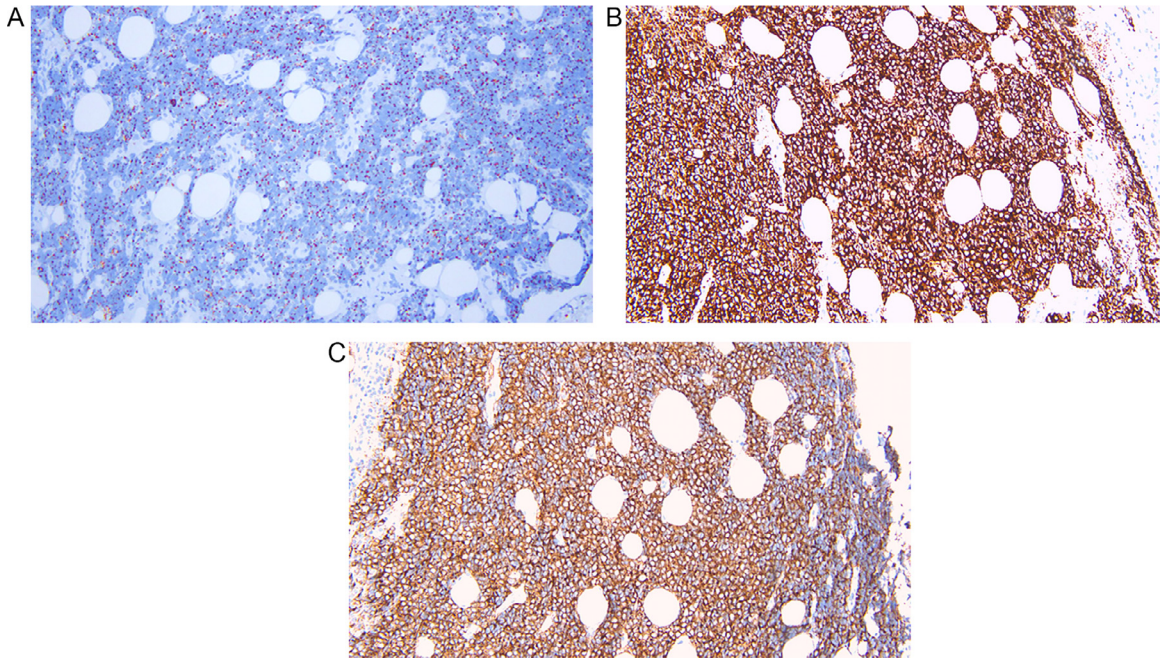


Fig. 4. **(A)** The cells show characteristic perinuclear dot-like staining with CK20 (× 200). **(B)** Strong cytoplasmic staining with CD56 (× 200) **(C)** and strong cytoplasmic staining with Synaptophysin (× 200). A high-resolution version of these slides for use with the Virtual Microscope are available as eSlides: VM05648, VM05649, and VM05650.

systemic immunosuppression, tobacco and alcohol use, and radiation therapy.[19]

MCC has been reported to occur on the skin, lip, oral mucosa, palatine tonsil, tongue, and rarely in a lymph node without an identifiable primary cutaneous lesion.[14,19] A recent review of the literature by Islam et al.[19] analyzed 26 reported cases; of these more than 50% occurred on the lip, suggesting a predilection for this site among cases of perioral MCC. This lesion is typically painless, firm to palpation, pink to bluish-red, and rarely larger than 5 cm.[4] The tumor is often subcutaneous; however it may ulcerate and involve the surface in advanced stages.[19] Given that the clinical presentation of MCC is often nonspecific, biopsy followed by immunohistochemistry is required for definitive diagnosis.

On microscopic examination, MCC is a poorly circumscribed dermal lesion that is usually separated from the epidermis by a thin grenz zone. The grenz zone contains apoptotic bodies and a lymphocytic infiltration. The tumor cells are poorly differentiated, small, round to ovoid cells containing scant cytoplasm, granular chromatin, high mitotic activity, and apoptotic figures. These tumor cells may infiltrate lymphatics, blood vessels, subcutaneous fat, fascia, and muscle.[20] Immunohistochemistry is necessary for an accurate diagnosis of MCC and to distinguish it from other small, blue, round cell tumors (SBRCTs).[18] The histopathologic differential diagnosis for a SBRCT in the head and neck region may include amelanotic melanoma, Ewing sarcoma (peripheral primitive neuroectodermal tumor), lymphoma, neuroblastoma, neuroendocrine carcinoma, poorly differentiated squamous cell carcinoma, primitive neuroectodermal tumor, rhabdomyosarcoma, and metastatic small cell carcinoma of the lung.[4,18] A highly sensitive stain used to help differentiate MCC from other SBRCTs is CK20, which stains the neoplastic cells of MCC in a unique perinuclear dot-like pattern. In addition to CK20, common MCC markers include CD56, chromogranin, synaptophysin, and neuron-specific enolase.[20]

MCC grows rapidly and follows an aggressive clinical course with poor prognosis and high rates of recurrence and metastasis. The rate of local recurrence is approximately 40%, and the rate of a recurrence with metastasis is 35%. For localized disease, the median survival is 26-30 months.[18] With lymph node involvement, the median survival is reduced to 18 months. With metastasis, the median survival drops significantly to 5 months. Half of patients succumb to their disease within 3 years of diagnosis. MCC was reported to be the second most common cause of death from nonmelanoma skin cancer.[21]

Despite the bleak outlook of this condition, complete spontaneous regression (CSR) has been infrequently reported. CSR of MCC was first reported by O'Rourke and Bell in 1986.[22] A review by Moghaddam found 46 cases of partial and CSR, even after recurrence or metastasis.[23] The mechanism for such regression is unclear. The review found a 4:1 female to male tendency for CSR, despite MCC having a higher incidence in men. Increased regression co-occurs with features of higher

apoptosis, dense lymphocytic infiltration around tumor cells, and antiretroviral therapy.[24] Interestingly, some authors have also suggested a better prognosis for cases of MCC involving MCPyV; however, the impact of MCPyV positivity in prognosis is still unclear.

Formal guidelines for the treatment of MCC have yet to be established because of the rarity of the tumor, and additional evidence is required to determine the standard of care. In all cases the tumor should be excised with wide surgical margins to avoid local recurrence. Two surgical protocols have been suggested: wide excision margins of 2.5 to 3 cm for cutaneous MCC to ensure negative margins, or margins of at least 1 to 2 cm followed by postoperative radiotherapy. A study by Tai et al.[25] also published surgical guidelines for MCC specific to the tumor location. This author also recommended lymph node dissection for sentinel lymph node involvement.[25] Although some report that chemotherapy provides no survival benefit, it has been suggested as a treatment modality for recurrent or inoperable lesions in patients with advanced metastatic disease.[14,19] Checkpoint inhibitor PD-L1 was used in the treatment of an MCC patient in 2018, and such interventions present an opportunity for future investigation.[26] The patient in this case report was treated with wide surgical excision and neck dissection as well as adjuvant chemotherapy. Despite therapies, she was found to have metastatic disease and shortly after succumbed to her illness.

## CONCLUSIONS

Merkel cell carcinoma is a rare but often devastating disease with a poor prognosis. Clinicians should closely monitor patients with significant risk factors, especially when working with an elderly population. Early detection and definitive diagnosis is of pivotal importance for prevention of metastatic disease and improved survival outcomes.

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