The Merkel Cell Carcinoma Challenge

A Review From the Fine Needle Aspiration Service

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Merkel cell carcinoma (MCC) is a highly aggressive neuroendocrine carcinoma of the skin that occurs primarily in elderly or immunocompromised patients. For this report, the authors reviewed the diagnostic challenges associated with MCC encountered on their fine-needle aspiration (FNA) service and also conducted an in-depth review of the literature on MCC. A computer search for patients who were diagnosed with MCC by FNA at the authors’ institution from 2006 to 2010 was conducted, and 5 patients were selected for cytologic and immunochemical analyses based on their varied and diagnostically challenging clinical presentations. The 5 selected patients had clinical findings commonly associated with MCC, including advanced age (4 of the 5 patients were ages 75-85 years) and a history of previous malignancies (3 of the 5 patients had a history of previous malignancy), and 1 patient was diagnosed with a concomitant low-grade lymphoma. The patients and their disease illustrated the protean clinical presentation of MCC and the clinical and cytologic challenges associated with this neoplasm. The current findings indicate the need for cytopathologists to be aware of the deceptive presentation of this neoplasm and its cytologic and immunochemical features to correctly diagnose this insidious neoplasm.

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KEY WORDS: Merkel cell carcinoma, fine-needle aspiration cytology, neuroendocrine carcinoma, polyomavirus, cytology.

INTRODUCTION

A newly recognized oncogenic virus, Merkel cell polyomavirus, has been implicated in the pathogenesis of Merkel cell carcinoma (MCC), a highly aggressive neuroendocrine carcinoma of the skin that occurs primarily in elderly and immunosuppressed individuals. The incidence of this lethal carcinoma has tripled during the past 15 years, and MCC has a mortality rate of 33%, exceeding that of melanoma. Although MCC can occur at any site, it has a predilection for the head, neck, and upper extremities, and it commonly presents as a firm, red-purple nodule on sun-exposed skin. Tumor cytologic features fall within the spectrum of "small blue cell tumors." MCC is easily mistaken for metastatic small cell neuroendocrine carcinoma, especially when metastasis represents the presenting lesion and the primary skin lesion is not apparent or overlooked. It is common for patients with MCC to have histories of other primary malignancies, resulting in additional diagnostic quandaries. The objective of this report was to review the diagnostic challenges associated with primary and metastatic MCC encountered on our fine-needle aspiration (FNA) service.

MATERIALS AND METHODS

A computer search for MCC diagnosed by FNA from 2006 through 2010 was done in the Division of Cytopathology, University of Texas Medical Branch. Five patients were selected based on having varied and diagnostically
challenging clinical presentations (see Table 1). Smears were performed on FNA material from all patients, including air-dried preparations stained with a rapid Romanowski method (Diff-Quik stain) for on-site evaluation and ethanol-fixed smears stained by the Papanicolaou method. Four patients had accompanying cell blocks. Cytomorphology and immunohistochemical stains (performed on the cell block from of 4 patients with commercial antibodies) were studied. An in-depth literature search on MCC was done and reviewed.

RESULTS

Patient 1

A woman aged 75 years presented with right inguinal lymphadenopathy (largest, 2.6 cm) and a 2 × 2 cm, bluish-red, firm, slightly raised area in subcutaneous tissue of the right leg. The latter was clinically interpreted as phlebitis or bruise. The patient had a remote history (>10 years) of renal cell carcinoma with metastasis to the pancreas and was status post right nephrectomy and Whipple pancreatectomy. There also was a remote history of high-grade vulvar intraepithelial neoplasia. FNA was performed on the right inguinal lymph node and revealed small round-to-oval cells with smudgy chromatin; this was interpreted preliminarily as metastatic small cell neuroendocrine carcinoma (Fig. 1A,B). Immunohistochemistry was performed, leading to diagnosis of metastatic MCC. Most neoplastic cells had crisp, dot-like perinuclear immunoreactivity with antibodies to cytokeratin 20 (CK20) and neurofilament (Fig. 1C,D). Similar dot-like staining also was observed with antibodies to anticytokeratin CAM 5.2 (CAM 5.2) (results not shown). There was weakly positive cytoplasmic immunoreactivity to synaptophysin, and trefoil factor 1 (TTF1) was negative. A diagnosis of metastatic MCC was rendered, leading to re-evaluation of leg lesion. A subsequent FNA confirmed that the leg lesion was MCC, and this was the presumed primary site. Subsequently, the patient was diagnosed with a fourth primary, which was squamous cell carcinoma of lung, and she currently is alive with recurrent MCC.

Patient 2

A woman aged 82 years presented with a left submandibular mass that measured 3.6 cm in greatest dimension and was tender to palpation; this was interpreted clinically as sialadenitis. She had a recent history of upper respiratory infection and sinusitis and had a long history of multiple squamous cell carcinomas of the skin. An FNA was

| Patient No. | Age, Sex | History of Prior Malignancy | Presentation and Pertinent History | FNA Results Effecting Further Outcome |
|------------|---------|---------------------------|-----------------------------------|--------------------------------------|
| 1          | 75 Woman | Remote history of metastatic renal cell carcinoma | Right inguinal lymphadenopathy; right leg mass clinically diagnosed as phlebitis or bruise | Inguinal lymph node FNA, preliminary diagnosis metastatic small cell carcinoma amended to MCC after immunostaining; prompted FNA of leg lesion with final diagnosis of primary MCC |
| 2          | 82 Woman | History of multiple squamous cell carcinomas of skin | Submandibular mass, clinically diagnosed as sialadenitis; separate 0.3 cm chin nodule | Submandibular node; MCC, metastatic; prompted biopsy of chin lesion with final diagnosis of MCC |
| 3          | 55 Man   | None                       | History of hepatitis C and generalized, diffuse lymphadenopathy/recent pathologic diagnosis of MCC of right arm with axillary lymph node metastasis | Left occipital lymph node FNA and flow cytometry revealed low-grade follicular lymphoma; MCC still suspected, prompting FNA of left cervical lymph node, for which FNA and flow cytometry revealed low-grade follicular lymphoma |
| 4          | 85 Man   | History of multiple squamous and basal cell carcinomas of skin | Elbow mass, axillary lymphadenopathy, multiple liver lesions, and 9-mm pancreatic lesion | Elbow mass and axillary lymph node, FNA revealed MCC; liver and pancreatic lesions were not biopsied |
| 5          | 84 Woman | None                       | A 1-y history of hyperpigmented thigh lesion followed by development of lymphadenopathy | FNA confirmed the presence of MCC, leading to resection and inguinal lymph node dissection |

Abbreviations: FNA, fine-needle aspiration; MCC, Merkel cell carcinoma.
requested by a consulting otolaryngologist and yielded abundant small, neoplastic cells with stippled chromatin, abundant mitoses, and inconspicuous nucleoli. Cell block preparation with immunochemical stains revealed perinuclear, dot-like cytoplasmic immunoreactivity for CK20, neurofilament, and CAM 5.2. Tumor cells did not have immunoreactivity for either chromogranin A or cluster of differentiation 45 (CD45 [leukocyte common antigen]). The diagnosis rendered was small cell neuroendocrine carcinoma, Merkel cell type. This diagnosis prompted subsequent evaluation and biopsy of the 3-mm chin lesion by a dermatologist, who described the lesion as a small, flesh-colored, subcutaneous nodule. The clinical differential included basal cell carcinoma and folliculitis. The final dermatopathologic diagnosis was MCC. The patient underwent excision of the submandibular mass, wide excision in the region of the chin lesion, and left neck dissection. She was readmitted 3 weeks later with abdominal pain and renal and liver failure, and she died in hospital.

Patient 3

A man aged 55 years presented with a 4-month history of a $5.0 \times 3.8 \times 2.6$ cm mass in his right posterior arm accompanied by a $3 \times 3$ cm right axillary lymph node. MCC with axillary metastasis was diagnosed on the basis of an excisional biopsy of both the arm lesion and the axillary lymph node. One month later, the patient had gross evidence of recurrence in the right arm at the excision site. Diffuse lymphadenopathy involving the neck, thorax, abdomen, and pelvis was discovered during a staging computed tomography scan and was presumed to represent disseminated MCC. FNA was performed from a palpable left occipital lymph node. Abundant small, blue cells were

**FIGURE 1.** (A,B) A fine-needle aspiration specimen from an inguinal lymph node reveals metastatic Merkel cell carcinoma (Papanicolaou stain; original magnification, $\times200$ in A, $\times400$ in B). (C,D) Neoplastic cells had positive staining for (C) cytokeratin 20 and (D) neurofilament.
observed at an onsite evaluation and were interpreted preliminarily as consistent with MCC; however, review of both Romanowski-stained and Papanicolaou-stained slides disclosed a monomorphic population of small, round-to-cleaved cells with coarse chromatin. On the basis of a new interpretation, FNA was repeated for flow cytometric immunophenotyping and disclosed a dominant population of CD5 (type I transmembrane protein)-negative, CD19 (B-lymphocyte antigen)-positive, CD20 (B-lymphocyte antigen)-positive, and CD10 (common acute lymphoblastic leukemia antigen)-positive population of lymphocytes. A final diagnosis of follicular lymphoma was made. Because of a persistent, strong suspicion for metastatic MCC by surgeons, a second, ultrasound-guided FNA was performed from a substernal lymph node and yielded a similar population of B lymphocytes. The final diagnosis from both sites was low-grade follicular lymphoma. Figure 2 compares the FNA morphology and immunostaining of the follicular lymphoma with the histologic appearance of the MCC. Human immunodeficiency virus (HIV) serology was negative. The patient was referred to the divisions of medical and radiation oncology. Local radiation to the arm lesion resulted in resolution of local recurrence, and adenopathy regressed with chemotherapy. The patient was lost to follow-up approximately 1 year later.

**Patient 4**

A man aged 85 years with history of multiple squamous and basal cell skin carcinomas presented with a baseball-sized left elbow mass, abdominal pain, and shortness of breath. Radiologic imaging disclosed a 6.5 × 6.1 soft tissue mass in the lateral elbow extending to the lateral...
condyle, possibly representing a gouty tophus. Concomitantly, a computed tomography scan of the thorax and abdomen was performed because of abdominal pain and disclosed large, left axillary lymphadenopathy measuring up to 2.8 cm, and FNAs of both the elbow mass and an axillary lymph node were performed. FNA material from both sites contained small, neoplastic cells with scanty cytoplasm and stippled chromatin that had positive cytoplasmic immunoreactivity for the pan-cytokeratin AE1/AE3 cocktail and CK20 and were negative for CD45. The final diagnosis was poorly differentiated carcinoma, favor MCC. The patient received comfort care and Do Not Resuscitate status. No further information is available.

**Patient 5**

A woman aged 84 years developed a mosquito bite-sized, hyperpigmented lesion on her right thigh that grew to a golf ball size within 1 year. She also noticed a progressively enlarging inguinal mass. MCC was diagnosed by punch biopsy of the thigh lesion performed at outside hospital. Positron emission tomography/computed tomography studies revealed a right thigh primary with a right inguinal mass. FNA of the inguinal lymph node contained abundant neoplastic cells with scanty-to-inapparent cytoplasm, abundant mitotic figures and apoptotic cells, and the presence of stippled chromatin. The diagnosis was rendered as neoplasm with neuroendocrine features consistent with metastatic MCC. She underwent surgical wide excision of the right thigh mass with superficial inguinal dissection. Follow-up positron emission tomography/computed tomography studies demonstrated the presence of abdominal, lung, and mediastinal nodules consistent with metastasis. The patient currently is receiving chemotherapy.

**DISCUSSION**

The 5 patients presented here illustrate some clinical findings that are commonly associated with MCC, including elderly age group and a history of previous malignancies. Four of the 5 patients in this series were elderly (ages 75-85 years). Three of the 5 patients had histories of previous malignancies, and 1 patient had a concomitant low-grade lymphoma. These patients also illustrate the protean clinical presentation of MCC and the clinical and cytologic challenges associated with this neoplasm. In 1 patient, it was believed that the primary was phlebitis or a bruise; and, in another patient, the primary was so tiny that it was overlooked. In a third patient, the lesion was interpreted radiologically as a gouty tophus. Cytologic misinterpretation also can occur, especially on the basis of rapid onsite evaluation. In Patient 3, a presumption of metastatic MCC was made from a lesion that proved to be follicular lymphoma. In Patient 1, MCC was interpreted initially as metastatic small cell carcinoma. The cytologist must learn to suspect MCC in FNA samples that demonstrate features of a high-grade neuroendocrine tumor in elderly individuals with histories of skin or extracutaneous malignancies, especially when there is no evidence of primary pulmonary or other visceral neoplasia. Perinuclear dot-like immunoreactivity with CK20 or neurofilament and negative staining for CD45 is useful. The sections below summarize the current MCC literature.

**Epidemiology**

MCC is a relatively rare cutaneous neuroendocrine neoplasm that was described first by Cyril Toker in 1972. MCC is most commonly located in the head and neck regions (37%-50%) and the extremities (40%-44%). Less commonly, MCC arises in the buttocks (9%-16 %) or trunk (4%-8%). Most cases occur in elderly patients (age range, 60-70 years); however, MCC may present earlier in immunosuppressed patients. There is 1 report of MCC in a patient aged 7 years. MCC occurs mainly in Caucasians, with few reports in African Americans and Polynesians. Most reports indicate a slightly higher incidence among men. Based on Surveillance, Epidemiology, and End Results Program data, the age-adjusted incidence rates (per 100,000 person-years) are 0.34 in men and 0.17 in women. The data also indicate an increasing incidence from 0.15 cases per 100,000 person-years in 1986 to 0.44 cases per 100,000 person-years in 2001, indicating that MCC incidence rates have increased 3-fold over the period from 1986 to 2001. MCC is more common in immunosuppressed patients than in the normal population. This includes those patients on chronic immunosuppressive therapy, patients with HIV, transplantation recipients, and patients with hematologic malignancies. MCC also reportedly has arisen with greater than normal frequency in patients who have other neoplasms. Chronic lymphocytic leukemia/lymphoma, B-cell lymphoma, and squamous carcinoma of the skin.
are the most frequently reported malignancies associated with MCC.3,23,18-22

Etiology

The exact etiology of MCC remains unclear but is likely multifactorial. The recently described Merkel cell polyomavirus (MCV) is suspected to be an agent important in the oncogenesis of MCC.1 MCV sequences have been detected in 8 of 10 cases (80%). In 75% of the positive cases, viral DNA was integrated within tumor genome in a clonal pattern, suggesting that MCV infection and integration preceded the clonal expansion of tumor cells.1 The role of such a viral factor is consistent with the previously reported observation that MCC often arises in patients with declining immune function, HIV infection, or immunosuppressive therapy.18,23 The impact of the presence of virus or viral load on the prognosis remains controversial and raises the possibility that it is a bystander.

Sunlight may also be a factor, because MCC is identified primarily in areas that receive actinic damage, suggesting that ultraviolet radiation (UV-B) may play a role.24 UV-B-induced cytosine-to-thymine transitions have been reported in MCC, supporting a role of sun exposure in the etiology of these tumors.11 Nevertheless, a significant number of tumors arise on nonsun-exposed regions.

The chromosomal abnormality most frequently reported in MCC is a deletion of the short arm of chromosome 1 (1p36).25 Changes observed on chromosome 1p suggest that 1 or more tumor suppressor genes play a role in the development of MCC, and certain individuals may be predisposed to develop this tumor.14,20 Deletions involving 1p35-36 are similar to those described for malignant melanoma, pheochromocytoma, and neuroblastoma, tumors known to originate from neural crest cells.26 Mutations in the tumor protein 73 (p73) gene (p53-like transcription factor) have been observed in MCCs. The p73 gene resides on 1p and has structural and functional homology similar to p53.11,25 Other studies examined the role of the B-cell chronic lymphocytic leukemia/lymphoma 2 (bcl-2) and p53 genes in MCC, and the results indicated that p53 and bcl-2 expression in MCC is variable and that either loss of function or excess function of bcl-2 and/or p53 may promote tumor development.14,27,28

Another frequently observed mutation that occurs in approximately 33% of patients involves loss of chromosome 10 or part of its long arm (10q).11 In 1 study, trisomy 6 was observed in 47% of patients.29 In another study, positive tyrosine-protein kinase Kit (c-Kit) status was reported in 95% of MCC tumors,30 generating interest in the tyrosine kinase inhibitor imatinib, which initially was designed to target the breakpoint cluster region/v-abl Abelson murine leukemia viral oncogene homolog (Bcr-Abl) fusion. However, Swick et al31 suggest that its effectiveness may be limited, because no c-Kit–activating mutations were observed in their series.

Clinical Features

MCC typically presents as a painless, solitary, pink-purple to red-brown, dome-shaped papule or plaque on sun-exposed skin of elderly or immunocompromised individuals. MCC occurs rarely in nonwhites. MCC is rare among African Americans (1%), and the anatomic location also differs, occurring more frequently on the lower extremities rather than on the head and neck.16,17 MCC size at presentation ranges from 0.2 cm to 23 cm; however, it usually measures ≤5.0 cm.32 The epidermis is usually intact, but more advanced lesions may become ulcerated.8 Rarely, as illustrated in our current series, the diagnosis of MCC is suspected clinically before biopsy.33 MCC tumors may present as plaques or subcutaneous masses without epidermal change. Most MCCs are diagnosed by dermatopathologists from biopsies submitted as suspected basal cell carcinoma, adnexal tumors, squamous cell carcinoma, pyogenic granuloma, cyst, lymphoma cutis, or melanoma.19,22,34 One-third of patients with MCC develop a local recurrence within after 1 year of excision.20,33 Spontaneous regression of cutaneous MCC has been described.35-38 In 10% to 20% of patients with metastatic MCC, the primary tumor is not identified. Differentiating MCC from primary Merkel cell-like small cell carcinoma of the salivary gland in this scenario can be almost impossible.

Cytomorphology

FNA can be a useful tool for diagnosing MCC but requires prior awareness of the tumor’s ability to mimic other neoplasms. Aspirate smears are moderately to highly cellular and contain relatively monomorphic, singly or loosely cohesive cells with scanty-to-inapparent cytoplasm resembling small cell neuroendocrine carcinoma. Cell
nuclei are rounded with smooth nuclear membranes, no indentations, and minimal nuclear molding and crush artifact. Scattered, small, cohesive groups are readily identifiable. Mitotic figures and apoptosis are apparent, but their frequency varies. Blue bodies (aggregates of intermediate filaments) similar to those observed in pulmonary small cell carcinoma, are sometimes present and are observed best on hematoxylin-and-eosin stains. These features may prove to be an enormous challenge because of the wide range of differential diagnosis, centering around the small round blue cell tumors; lymphoma, peripheral neuroectodermal tumors, rhabdomyosarcomas, and other skin-associated tumors like melanoma, basal cell carcinoma, and adnexal tumors.39

Ancillary Studies: Immunohistochemistry

Differentiating MCC from its mimics requires the use of immunohistochemistry (Tables 2 and 3). Immunohistochemical analysis is best done on formalin-fixed cell block preparations; however, smears and Cytospin preparations have been used.

MCC tumor cells typically express both epithelial and neuroendocrine markers. Several types of epithelial markers react with MCC, such as CAM 5.2, AE1/AE3, CK20, tumor protein p63 (34BE12), and epithelial membrane antigen (EMA).40-43 Low-molecular-weight cytokeratins (CK8, CK18, and particularly CK20) are useful for diagnosis. The majority of MCCs (75%-90% of tumors) are at least focally positive for CK20, typically in a paranuclear, dot-like pattern.40-42,44 CK20 reportedly is the most sensitive and specific marker for detecting micrometastases in sentinel lymph node biopsies.30 Neuroendocrine markers (chromogranin, synaptophysin, CD56, neural cell adhesion molecule, and neurofilament) also are positive in most tumors.45-47 Recently, reactivity with

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TABLE 2. Mimics and Diagnostic Pitfalls

| Neoplasm                        | Problem                                      | Solution                                                                                           |
|---------------------------------|----------------------------------------------|----------------------------------------------------------------------------------------------------|
| Lymphoma                        | MCC morphology can be mistaken as lymphoma   | CK20 may rule out most lymphomas, but be aware of keratin-positive lymphomas; look for lymphoglandular bodies and chunky chromatin in lymphomas, and consider adding a neuroendocrine marker; flow cytometry studies |
| Pulmonary small cell carcinoma  | Both may express CK20                        | TTF-1 is typically positive in the pulmonary SMCC and negative in MCC; CK20 "dot-like" positivity in MCC |
| Extrapulmonary small cell carcinoma | Share similar immunophenotype; both express dot-like CK20 positivity | Clinical information and work up                                                                 |
| Cutaneous PNET/Ewing sarcoma    | Both are often Fli-1 and CD99 positive        | CK20 is positive in MCC and negative PNETs                                                        |
| Amelanotic melanoma             | Epidermotropic MCC can mimic melanoma and also is rarely S100-positive. | CK20 is positive in MCC and negative in melanoma                                                  |
| Basal cell carcinoma            | Can occur along with MCC                     | CK20 is positive in MCC and negative in BCC; MCC does not have palisading                         |
| Rhabdomyosarcoma                | Small round cells                            | Desmin-positive, myogenin-positive, and keratin-negative                                          |

Abbreviations: BCC, basal cell carcinoma; CD99, cluster of differentiation 99 (MIC2; a single-chain type-1 glycoprotein); CK20, cytokeratin 20; Fli-1, Friend leukemia virus integration 1; MCC, Merkel cell carcinoma; MSCC, metastatic small cell carcinoma; PNET, primitive neuroectodermal tumor; S100, a calcium-binding protein; SMCC, small cell Merkel cell carcinoma; TTF-1, trefoil factor 1.

TABLE 3. Immunohistochemistry of Common Mimics

| Diagnosis                      | CK20     | CK7    | LCA     | S100  |
|--------------------------------|----------|--------|---------|-------|
| Merkel cell carcinoma          | Positive | Negative | Negative | Negative |
| Small cell carcinoma           | Negative | Positive | Negative | Negative |
| (lung)                         |          |         |         |       |
| Lymphoma                       | Negative | Negative | Positive | Negative |
| Melanoma                       | Negative | Negative | Negative | Positive |

Abbreviations: CK, cytokeratin; LCA, leukocyte common antigen; S100, a calcium-binding protein.
paired box protein 5 (PAX-5), c-kit (75%-95%), and terminal deoxynucleotidyl transferase (Tdt) has been described.\textsuperscript{28,29,48-51} Flow cytometry is useful if there is a history of or suspicion of coexisting lymphoma, as illustrated in our Patient 5.

**Staging and Treatment**

Patients may be staged according to the American Joint Committee on Cancer staging system for skin cancer or according to the similar, 4-tier system from Memorial Sloan-Kettering Cancer Center\textsuperscript{5} (Table 4). The MCC staging system is based on tumor size, lymphatic spread, and distant metastasis and is used to determine primary, adjuvant, and palliative therapy.\textsuperscript{11,52,53} Specific survival probabilities for patients with MCC depend on their disease stage at the time of presentation. And, as expected, disease stage correlates with survival. On the basis of Surveillance, Epidemiology, and End Results data,\textsuperscript{54} the 10-year relative survival rate for patients with localized MCC was 71%, whereas the 10-year relative survival rate for patients with regional disease was 47.8%, and the rate for those with distant disease was 20.1%. The 10-year relative survival rate based on tumor size is 61% for patients with tumors \( \leq 2 \text{ cm} \) and approximately 40% for patients with tumors \( > 2 \text{ cm} \). Recurrence reportedly is common at a rate of approximately 40%.\textsuperscript{5,55}

Even with treatment, MCC has a strong propensity toward local recurrence, lymphatic spread, and distant metastasis.\textsuperscript{56,57} The optimal treatment for patients with MCC remains unclear. Current treatment includes Mohs or wide surgical excision and regional lymphadenectomy of any suspicious lymph nodes.\textsuperscript{5} Many protocols also advocate adjuvant chemotherapy and radiation therapy.\textsuperscript{58} Currently, there is increasing interest in staging by imaging regional lymph nodes with lymphatic mapping using colloidal technetium-99 and sentinel lymphadenectomy.\textsuperscript{11,21}

**Prognostic Indicators**

Findings that had a statistically significant correlation with poor outcome included tumor size \( \geq 5 \text{ mm} \), depth of tumor invasion, diffuse growth pattern, heavy lymphocytic infiltration, increased mast cell count, and lymphovascular invasion.\textsuperscript{4,6,59,60} Factors that are associated with an improved prognosis include tumor size \( < 2 \text{ cm} \), women, and local radiation treatment.\textsuperscript{61} Patients who have tumors located in the upper extremities fare better than those who have tumors located in the head and neck, trunk, and lower extremities.\textsuperscript{9,19} Patients who have tumors on mucosal surfaces also appear to have a worse prognosis, probably because of greater access to vascular and lymphatic channels.\textsuperscript{62} Distant metastasis indicates a very poor prognosis and is the most important predictor of survival.\textsuperscript{24} The most common metastatic sites are lymph nodes followed by liver, bone, brain, lung, skin, and gastrointestinal tract.\textsuperscript{24} Spontaneous regression has been noted in some patients with MCC.\textsuperscript{35-38} Apoptosis and T-cell immune response involvement has been suggested as the mechanism behind tumor regression.\textsuperscript{37}

In conclusion, the incidence of MCC is rising: It is diagnosed most commonly in elderly or immunocompromised patients, and it has higher mortality than melanoma. Because of its nonspecific clinical presentation, MCC is rarely suspected before biopsy. Cytopathologists need to be aware of the deceptive presentation of this neoplasm and its cytologic and immunochemical features to correctly diagnose this insidious neoplasm.

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**TABLE 4. Four-Tier Staging System for Merkel Cell Carcinoma**

| Stage | Diagnosis | Localized Disease | Lymph Node | Metastasis |
|-------|-----------|------------------|------------|------------|
| I     | Primary lesion <2 cm | Positive | Negative | Negative |
| II    | Primary lesion >2 cm | Positive | Negative | Negative |
| III   | Positive lymph node | Positive/negative | Positive/negative | Negative |
| IV    | Distant metastasis | Positive/negative | Positive/negative | Positive |
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