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REVIEW ARTICLE

Merkel cell carcinoma: clinicopathological aspects of an unusual neoplasm

I.E. Liapakis[1], D.P. Korkolis[2], A. Koutsoumbi[3], G. Kokkalis[1], G. Gherardini[4], P.P. Vassilopoulos[2]

[1]Department of Plastic and Reconstructive Surgery, [2]1st Department of Surgical Oncology, [3]Department of Pathology, Hellenic Anticancer Institute, "Saint Savvas" Hospital, Athens, Greece; [4]Plastic Surgeon, Rome, Italy

Summary

Merkel cell carcinoma (MCC) is a rare, aggressive cutaneous cancer that predominately affects elderly Caucasians with fair skin and has a propensity for local recurrence and regional lymph node metastases. It can occur on the face, the trunk, the genitalia, and the perianal region. The median age of the patients is 69 years, but it may occur earlier and more frequently in immunosuppressed patients. MCC usually arises in the dermis and extends into the subcutis. It may be difficult to accurately diagnose MCC by light microscopy alone and ancillary techniques, including electron microscopy and immunohistochemistry, may be necessary for a definitive diagnosis. The management of MCC is dependent on the stage of the disease and is hampered by its rarity and lack of randomized trials. Nonetheless, for localized disease most guidelines include wide local excision of the primary tumor either alone or followed by radiation therapy. Sentinel lymph node biopsy can be helpful in staging and prognosis, but its benefit in survival remains to be seen. Systemic chemotherapy may be considered as an adjuvant following surgery or to treat locoregional or distant disease. The prognosis of MCC is variable. In patients with localized disease the course is indolent and is well-controlled with local excision alone. On the other hand, many tumors are aggressive and have a tendency for locoregional recurrence and distant metastases. Such patients have a grim prognosis, with a median survival of 9 months. Successful outcome most often is seen in patients with early diagnosis and complete excision.

Key words: Merkel cell carcinoma, metastases, recurrence, survival

Introduction

MCC is a highly malignant skin cancer. The tumor was first reported by Toker in 1972 [1], although the Merkel cell itself was described more than 100 years ago. Situated at the dermo-epidermal junction, the Merkel cell is postulated to be a slowly adapting type-I neuroreceptor that mediates the sense of touch and hair movement [2]. It is now believed that it is of epidermal origin, although it shares features of neuroendocrine cells [3]. The cell is easily identified ultrastructurally by the dense core granules or by immunohistochemical methods [4].

Although the Merkel cell is located mainly in the epidermis, the majority of MCCs appear to arise in the dermis and may extend into the subcutaneous fat and muscle [4-6]. Typically it presents as a solitary nodule of pink to violaceous or reddish-brown colour and tends to grow rapidly, within 1 year [6-11]. Usually the primary lesion is < 2 cm in diameter, but it may vary in size from few millimetres to several centimetres [6]. A broad differential diagnosis exists that includes squamous cell carcinoma, basal cell carcinoma, adnexal tumors, lymphoma, melanoma, and cutaneous metastases of small-cell lung carcinoma [4,6-9].

MCC occurs most commonly in the 6th to 8th decades of life [5,10,11]. There is no uniform agreement on the sex distribution of this tumor [5,6,10]. Although the etiology is unknown, the most common site of occurrence is the sun-exposed head and neck region, where the primary tumor is found in 50% of the cases

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Author and address for correspondence:

Ioannis E. Liapakis, MD, PhD
65 Xanthipou Street
155 61 Cholargos
Athens
Greece
Tel: +30 210 6516332
Fax: +30 210 6420146
E-mail: liapjo@yahoo.com

[6,12-14]. Tumors of the extremities occur in ~40% of the cases, while the trunk is less commonly affected [6,12-14]. This aggressive skin cancer has a high incidence of local recurrence (26-77%), regional metastases (31-66%), and widespread dissemination (26-54%) [8,10, 12,14-17].

Diagnosis

Diagnosis of MCC was previously based on electron microscopy findings, but immunohistochemical staining alone can now reliably confirm the diagnosis (Figures 1, 2). This is based on demonstration of the endocrine marker neuron-specific enolase (NSE), on a paranuclear expression of simple keratins and on the absence of S100 protein and leukocyte common antigen [7,15,17]. Neurofilament proteins, which are not a feature of the normal Merkel cell, are also present in MCC [18].

Clinical indicators that are commonly stated to indicate a high-risk lesion include tumor size > 2 cm, evidence of nodal or systemic metastases at diagnosis, and location in the head and neck region [13]. Histologically, a high mitotic index (more than 10 mitoses per high power field) is also regarded as an unfavorable prognostic factor [6]. Shaw and Rumball documented 66% mortality in a series of patients who developed locoregional recurrence [13].

Staging

Current diagnosis and staging of MCC is significantly improved by the introduction of the chromogranin A (CgA) assay in plasma or serum as a tumor marker. Due to its capacity to express somatostatin receptors, it can be detected *in vivo* with ^{111}In-pentetreotide scintigraphy (Ostreoscan) and by the use of somatostatin receptor scintigraphy (SRS) for tumor localization. SRS proved to be more sensitive than CgA, with equivalent specificity. Tumor differentiation influences the sensitivity of SRS and CgA analysis. In addition, the plasma CgA level is related to tumor secretory activity. Nevertheless both SRS and CgA should be considered useful tools in the diagnostic work-up of MCC patients [19,20].

MCC is a potentially aggressive tumor with propensity for both local recurrence and systemic spread [21]. Therefore accurate staging is necessary to make the right choice for treatment. In addition to Kwekkeboom et al., other authors observed the detection of metastatic MCC by ^{111}In-labelled octreotide scintigraphy in individual cases, inferring that these tumors express somatostatin receptors [22-25].

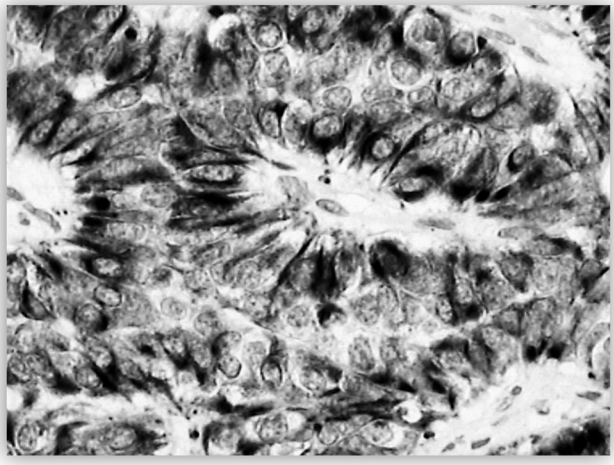

Figure 1. Metastatic Merkel cell carcinoma exhibiting characteristic punctate perinuclear staining with antineurofilament protein antibodies (Immunohistochemistry, monoclonal Abs Ki67, Dako, ×100).

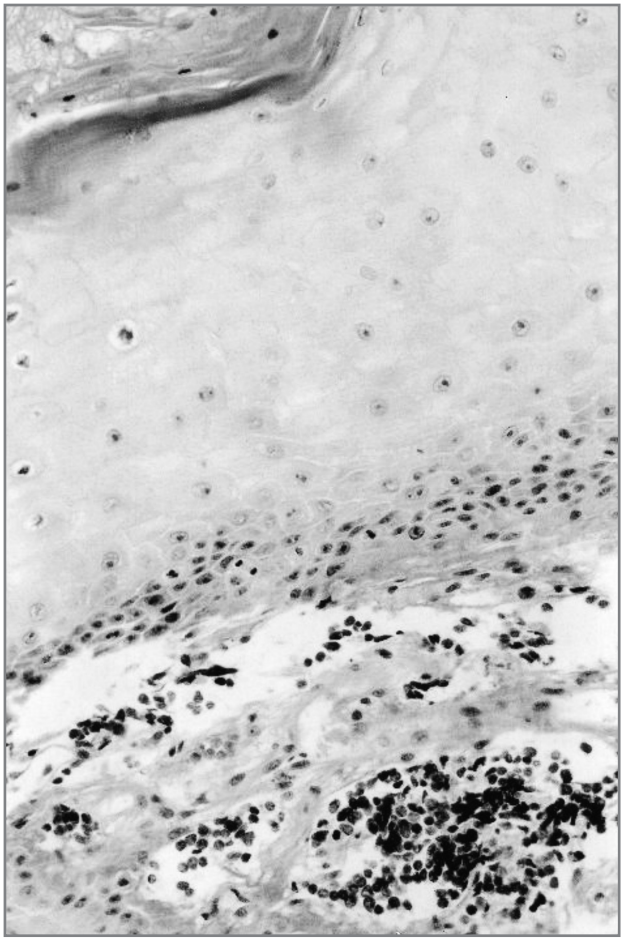

Figure 2. Merkel cell carcinoma of facial skin illustrating hypercellularity, scant cytoplasm, nuclear molding, stippled chromatin, apoptotic bodies, and scattered mitotic figures (H&E ×150).

Immunoreaction of Merkel cells with the antibody against the human somatostatin sst 2a receptor was described by Hartschuh et al. in 2000 [26], supporting the expectation of Kwekkeboom et al. [22] that MCCs have somatostatin receptors and can be visualized by ^{111}In-octreotide scintigraphy. However, the actual value of ^{111}In-octreotide scintigraphy in detecting MCC metastases is still not clear.

Recently, Guitera-Rovel et al. reported 20 patients with MCC, who were investigated by ^{111}In-octreotide scintigraphy [27]. In their study 4 of 5 primary tumor sites, 6 of 8 lymph node sites, no skin metastases (14 sites in 2 patients), 2 of 3 thoracic metastases and none of the 2 hepatic metastases were found. The ^{111}In-octreotide scintigraphy was not recommended for routine evaluation.

The possibility of false-positive ^{111}In-octreotide scintigraphy should be seriously taken into consideration. Other techniques such as FDG-PET and MIBG scans need to be evaluated for their usefulness for diagnosis and follow-up of patients with MCC. Furthermore, PET with ^{68}Ga-DOTATOC seems likely to be an interesting technique for the imaging of somatostatin receptor-positive tissue.

Treatment

Treatment guidelines are not well defined, mainly due to the small number of cases in most series, which prohibits a randomized clinical trial. Surgery is the mainstay of treatment, with wide local excision (>3 cm) of the primary tumor, together with regional lymph node dissection as indicated.

Nodal treatment (clinically node-negative)

Local excision without regional lymphadenectomy, even in the setting of a small primary lesion, does not address the high risk of subclinical nodal disease. In one series, there was a 44% rate of nodal relapse in patients with lesions < 10 mm in diameter [28]. In an Australian study of patients treated with local excision subsequent development of regional relapses was observed with lesions of 5-10 mm and >10 mm in size (33% and 50%, respectively) [29]. Predicting subclinical nodal disease based on a negative clinical examination is rather hazardous, with one series reporting a 23% rate of pathologically involved nodes in clinically node-negative necks following nodal dissection, but notably a 44% rate of nodal recurrence in patients staged clinically as node-negative but without elective lymphadenectomy [30]. In a review of the literature 181 patients underwent local surgery without nodal dissection, and a total of 83 (46%) experienced nodal relapses [31]. Similarly, the authors of another study reported 50% nodal relapse rate in patients treated with surgery alone compared to 19% in patients receiving adjuvant radiotherapy [32]. Therefore, the argument for local excision only as adequate treatment for a patient with clinically localized MCC is difficult to defend, based on the high rate of regional relapses, which in turn usually portends a poor outcome.

Sentinel node biopsy

Sentinel node biopsy (SNB) may improve the ability to detect subclinical nodal metastases although its exact role is unclear. In a series of 10 patients with MCC located in the head and neck, SNB was performed using both hematoxylin & eosin (H&E) staining and CK-20 immunostaining [33]. Two patients were positive (H&E-negative but CK-20-positive) and received nodal irradiation, remaining disease-free. One patient of 8 (12%) developed a regional failure despite a negative SNB (H&E-negative and CK-20-negative). The authors, therefore, reported a 12% false-negative rate in this small study but did highlight the potential benefit of incorporating CK-20 into the identification of micrometastases. In a small meta-analysis of patients with MCC undergoing SNB, 60 patients were identified from the literature [34]. The authors reported that 40/60 (67%) patients with a negative SNB had no microscopic nodal disease, with almost all of them (97%) remaining relapse-free, although the median follow up for this group was only 7.3 months. In keeping with the high rate of subclinical metastases, 33% of patients had positive SNB. One third of this node-positive group subsequently developed locoregional or distant relapses highlighting the unfavorable outcome of patients with node-positive MCC. Of interest 15 SNB-positive patients, who proceeded to node dissection (±radiotherapy and/or chemotherapy), remain free of regional recurrence compared to 75% regional relapses in those who were SNB-positive without lymph node dissection. The qualified conclusions from this meta-analysis were that SNB-negative patients probably should not receive adjuvant treatment based on the low rate of relapse. Although there may be some evidence to support this view, further larger and prospective studies are needed to validate the results from these mainly small case series.

Nodal treatment (clinically node-positive)

In patients presenting with nodal disease, radical surgery and adjuvant locoregional radiotherapy are recommended. One study demonstrated improved regional control with this multimodality approach compared to nodal dissection alone (14 vs. 43%) [29]. In a large single-institution study, patients who were clinically negative, but had pathologically involved nodes post-nodal dissection, did not experience any significant difference in nodal recurrence with the addition of adjuvant radiotherapy (15 vs. 8%; p = 0.19) [30]. However, when comparing regional recurrence based on treatment in patients with both clinical and pathological nodal disease, the nodal recurrence was 13% with adjuvant radiotherapy vs. 26% without radiotherapy (p = 0.13). Despite the fact that the difference did not reach statistical significance, the rate of recurrence is of clinical relevance. Patients with regional relapses are usually incurable, either because of untreatable regional disease or the concurrent or subsequent development of distant metastases. In the case of a patient presenting with previously untreated unresectable nodal disease, high-dose radiotherapy (~60 Gy) may downstage the disease so that nodal dissection could follow, if regression leads to improved operability.

Definitive radiotherapy

MCC is a radiosensitive small-cell carcinoma, treated with moderate radiotherapy doses in the range of 45-60 Gy. In some cases, patients were treated with definitive radiotherapy and were cured [28, 29, 31, 35, 36]. In a French study, 9 patients with node-negative MCC were treated with radiotherapy alone (median dose 60 Gy) with median duration of follow up of 3 years; none of them relapsed, although 3 have died from unrelated causes [36]. In one series, 6 patients, most of them with advanced MCC and treated with definitive radiotherapy, attained complete or partial tumor response, although most died from subsequent distant relapse [29]. Similarly, in a series of 34 patients that had included 8 irradiated with macroscopic disease, all but one achieved and maintained complete tumor response [35]. Furthermore, in a study of 27 patients, 5 developed progressive disease while waiting for adjuvant radiotherapy [37]. Despite this, on completion of radiotherapy 4 achieved complete response. Although such anecdotal cases do not add convincing evidence to support a definitive role for radiotherapy in the majority of patients, such cases do highlight the radiosensitivity of MCC to moderate-dose radiotherapy even in the setting of macroscopic disease.

Adjuvant radiotherapy

With few exceptions, the majority of the studies have reported a marked benefit in locoregional control with the addition of adjuvant radiotherapy. In one series, the authors report a 100% relapse rate (mainly regional) in 38 patients treated with surgery alone, compared to only 29% in those receiving adjuvant radiotherapy (50 Gy in 20-25 fractions) [38]. In a similar study of 34 patients treated with wide local excision, 59% experienced regional relapses as the first site of relapse, compared to 27% regional relapse rate in 26 patients treated with local surgery and adjuvant radiotherapy (46-66 Gy to primary site and draining lymphatics) [19]. In a series of patients treated with surgery alone (n = 37), most (89%) experienced local (9/37), locoregional (7/37) or regional (17/37) relapses compared to only 5/12 (42%) patients relapsing after surgery and radiotherapy (50-55 Gy) [30]. The authors of another study recommended postoperative wide-field locoregional radiotherapy based on the results from 31 patients. In that study, the improvement in locoregional control was significant on Cox regression analysis (hazard ratio 0.35; 95% confidence interval 0.13-0.91) for patients treated with surgery and adjuvant radiotherapy compared to surgery alone [32]. Local relapse was reduced from 36% to 6% and regional relapse from 50% to 19%, respectively, with the addition of adjuvant radiotherapy. A University of Florida series of 34 patients treated mainly with surgery and radiotherapy also documented a low (6%) local recurrence rate, although 38% of patients ultimately developed distant metastases [35]. An Australian prospective study reported a low (17%) locoregional relapse rate in high-risk patients treated with radiotherapy and chemotherapy [39]. In another Australian study 10/16 patients treated with surgery alone experienced locoregional relapse compared to 0/11 treated with surgery and adjuvant radiotherapy [40]. In a Westmead Hospital study with 86 patients, 37% of them treated with surgery (including 7 with nodal dissections for clinical disease) experienced regional relapse compared to 18% treated with surgery and adjuvant radiotherapy (median dose 50 Gy) [29].

Targeted radiotherapy

The advanced age of patients often impedes ad-

equate therapy. (90)Y-DOTATOC is a novel radiolabeled somatostatin analogue containing the active octapeptide of somatostatin. It is very well tolerated and offers the option of treating somatostatin receptor-positive tumors by targeted radiotherapy [41].

Chemotherapy

Based on the fact that the cause of death is mostly due to eventual systemic metastases, the addition of systemic chemotherapy is reasonable. Multiple chemotherapeutic agents, typically in combination, used in small-cell carcinoma of the lung, have been used as primary or adjuvant treatment of metastatic MCC, with moderate response. These include cyclophosphamide, doxorubicin, epirubicin, etoposide, cisplatinum, vincristine, methotrexate, 5-fluorouracil, streptozotocin, carboplatinum, and dacarbazine [42-48]. In one study of 16 patients receiving systemic chemotherapy the objective response was rate was 66%, although the duration of response was relatively short-lived [46,47]. Fenig and coworkers reported a complete response in 4 of 8 patients with advanced MCC who were treated with induction chemotherapy followed by consolidation radiation therapy [49]. The chemosensitivity of MCC was addressed by Kearsley et al., who reported the highest sensitivity in order of frequency to doxorubicin, epirubicin, cyclophosphamide, etoposide, and cisplatinum [50]. However, in the group of patients with distant metastases, most still died within 1 to 2 years, even though some had responded to chemotherapy. Indeed, more effective and durable chemotherapeutic agents are needed.

Discussion

MCC is an uncommon aggressive skin tumor. This cancer has a preponderance for sun-exposed areas of the body, suggesting an association with actinically damaged skin [6,51,52]. The odds for locoregional recurrence are high and both regional and systemic spread are associated with this tumor, which usually occur within 2 years from diagnosis. Documented haematogenous spread to liver, bone, brain and lung is supported by the sites of metastases in many studies, although Hitchcock et al. also noted that the retroperitoneal lymph nodes are commonly involved [7]. There are reports of occasional in-transit cutaneous nodules [5,14,17] occurring secondary to tumor foci in dermal lymph vessels.

Because of the frequent lymphatic dissemination leading to satellite lesions and recurrences, the natural history and pattern of spread of MCC has been likened to melanoma [13]. However, the overall prognosis of MCC is significantly worse than malignant melanoma [16]. The mortality from MCC has been quoted between 25 and 61% [8,10,12,14-17].

Surgery has been the mainstay of treatment of MCC in the past, with some authors advocating local excision together with elective or regional lymph node dissection as the only form of treatment [16,17]. Wide surgical excision of the primary tumor has been advocated in view of the high incidence of local recurrence [8,13,16,17]. Lateral margins of at least 2-3 cm are recommended [8,13,16]. However, as the primary tumor most often occurs on the head and neck and patients are commonly elderly, wide local excision with major reconstructive surgery may be impractical. Because of the high incidence of regional metastases, prophylactic dissection of draining lymph nodes is also recommended by some authors [13,14,53]. A recent study has shown that local excision alone had a projected 5-year survival rate of 58% compared to 88% in those treated with local excision and prophylactic or therapeutic lymph node dissection [53]. Meeuwissen et al. documented the superiority of surgery plus radiotherapy over surgery alone for the locoregional control of primary or recurrent disease [54]. Others have also noted the benefit of postoperative irradiation in the locoregional management of MCC [55-58].

It is suggested that after primary excision the radiation field should encompass the primary tumor bed with generous margins, as well as in-transit and draining lymphatics [6,8,9,52,57]. Radiotherapy alone is generally disappointing and is commonly used for palliation in advanced or inoperable disease [13]. One study, however, has shown complete locoregional tumor response to irradiation alone in one patient with unresectable locoregional disease [52].

Usually used in the setting of advanced disease, chemotherapy has been shown to produce rapid but mostly short-lived responses [59,60]. There are, however, reports of occasional durable remissions following chemotherapy, which suggests that systemic treatment should be offered to patients of good performance status with advanced MCC [60-62]. This patient population is more prone to toxicity from chemotherapy [63] because of their advanced age and consequently the cytotoxic regimen used must be well tolerated by elderly patients. Carboplatin and etoposide are usually well tolerated, with the principal toxicities being alopecia and myelosuppression. It is possible to predict the extent of myelosuppression induced by carboplatin by using a formula based on glomerular

filtration rate and this should be incorporated in dose calculation [64,65]. Although the present role of adjuvant chemotherapy is undefined, the high frequency of systemic relapse may warrant further review of this therapeutic modality after completion of definitive local treatments.

Conclusion

MCC carcinoma is an aggressive skin cancer with a high incidence of metastases, locoregional recurrences and high mortality rate. This skin tumor occurs mainly in the elderly, it is commonest on sun-exposed areas and it is both radiation- and chemotherapy-sensitive. Wide local excision and prophylactic lymph node dissection is practical, in view of the high incidence of local recurrence and regional metastases. Adjuvant radiation treatment can be used in conjunction with surgery to improve locoregional control and survival. Although chemotherapy may be helpful, particularly in the palliative setting, its role in adjuvant treatment is unclear. In view of the high incidence of recurrences and metastases, particularly in the first 2 years, all patients should be routinely followed up on a regular basis.

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