Merkel cell cancer of the skin

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Merkel cell carcinoma (MCC) is a rare malignant cutaneous tumor of the elderly with rapidly growing skin nodules found predominantly on sun-exposed areas of the body. The vast majority of patients present with localized disease, while up to 30% have regional lymph node metastases. Despite local excision and the incidence of local recurrence, regional lymph node metastases and distant metastases is high and usually occurs within 2 years of primary diagnosis. The optimal treatment for patients with MCC remains unclear. The best outcome is achieved with multidisciplinary management including surgical excision of primary tumor with adequate margins and post-operative radiotherapy (RT) to control local and regional disease. Patients with regional nodal metastases should be treated with lymph node dissection plus RT. Adjuvant chemotherapy (CT) should be considered as part of the initial management. In case of metastatic disease CT based on regimens used for small-cell lung cancer is the standard treatment of care.

Key words: chemotherapy, Merkel cell carcinoma, prognosis, radiotherapy, surgery

introduction

Merkel cell carcinoma (MCC) is a rare malignant cutaneous tumor of the elderly that is characterized by an aggressive course with regional nodal involvement, distant metastases and a high rate of recurrence. MCC was first described by Toker in 1972 [1] as trabecular carcinoma of the skin and, since then, has also been considered as cutaneous APUDoma, neuroendocrine tumor of the skin, Merkel cell tumor, primary small cell carcinoma of the skin, primary undifferentiated carcinoma of the skin, anaplastic carcinoma of the skin and murky cell carcinoma [2]. MCC and neuroendocrine carcinoma of the skin are the most widely used terms and may best reflect postulated origin and immunocytologic characteristics of this neoplasm.

epidemiology

Every year in the United States, there are approximately 470 new recorded cases. The estimated annual incidence according to US Surveillance data, Epidemiology, and the End-Results Program is 0.23 per 100 000 people for whites [3]. From 1987 to 2001, the Finnish Cancer Registry recorded 141 cases of MCC in a population of 5 000 000, which gives an annual prevalence of 0.2 cases per 100 000 [4]. The incidence in blacks (0.01 cases per 100 000) as well as for Polynesians seems to be lower. Both sexes are affected, but there seems to be a male predominance (2.3:1) [3, 5–7]. In some series the incidence in women was reported higher than that in men [8, 9]. MCC occurs in elderly patients, with an average age of diagnosis at 69 years (range 7–104 years). Only less than 5% of cases occur before the age of 50 years [7, 9–13].

clinical manifestation and diagnosis

Most patients present with rapidly growing, painless, firm, non-tender, dome-shaped red, occasionally ulcerated skin nodules, which have a red or bluish color, measuring up to several centimeters, on predominantly sun-exposed areas of the body [11]. The overlying skin is smooth and shiny, sometimes exhibiting ulcerative, acneiform or telangiectatic features [14]. However, the clinical feature of Merkel cell tumor is typically not acneiform. MCC can spread through the dermal lymphatic system, resulting in the development of multiple satellite lesions. MCC involves predominantly the head and neck (>50% of cases) [9, 15]; it involves the extremities in 40% of cases and the trunk in less than 10% of cases [2, 16–20]. On the face, the eyelids are involved more frequently [21]. MCC involving other sites not exposed to sunlight has been reported in a small percentage of cases [22–24]. At presentation most patients with MCC present with localized disease (70%–80%), 9%–26% have regional lymph node metastases and 1%–4% distant metastases [11, 18]. Despite local excision, the incidence of local recurrence (27%–60%), regional lymph node metastases (45%–91%) and distant metastases (18%–52%) is high and usually occurs within 2 years of primary diagnosis [11, 25, 26]. The majority of patients die from distant metastases involving liver, bone, lung, brain or distant lymph nodes [11, 26, 27]. Because the early course of MCC is asymptomatic, diagnosis may be delayed until the detection of regional lymphadenopathy and distant metastases. Symptoms are related to local spread or

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to involvement of regional lymph nodes. Superior vena cava syndrome due to obstruction by tumor has been reported [28]. Spontaneous regression of the primary lesion has been reported [29] and 20%–30% of patients present without obvious primary lesion. Patients who present with no obvious primary tumor seem to have a better prognosis [30, 31]. The differential diagnosis of MCC includes basal cell carcinoma, lymphoma, melanoma and squamous cell carcinoma, with MCC usually being overlooked [14]. The correct diagnosis of MCC is not made until tissue sampling and pathologic evaluation are performed.

staging and prognosis

There is no universal accepted staging system for MCC, but tentative classification relies on clinical manifestation and includes: stage I, localized cutaneous involvement (IA: ≤2 cm, IB: >2 cm); stage II, regional nodal involvement; stage III, systemic metastases [7, 32]. Even though the diagnosis of MCC is exclusively pathologic, imaging is useful for staging, surgical guidance, therapeutic management and follow-up. This staging system allows therapeutic approaches according to the stage: stage I and II should be treated with curative intent and stage III as a palliative treatment.

The most important prognostic factor for survival and development of distant metastases is the presence of lymph node involvement [6, 33]. In the series of Poulsen et al. [30], most important predictors for local control and survival were the tumor site and the presence of regional lymph node metastases. Morrison et al. [34] reported that the median survival of patients with lymph node metastases was 13 months and for those without lymph node involvement it was 40 months. Other reported poor prognostic factors include location on the lower extremities [31] because of difficulties in local control and the high incidence of local failure due to the poor blood supply in the legs, which limits big surgical procedures, and the subsequent poor tolerability of radiotherapy (RT) by the elderly. Furthermore, they include tumor size ≥2cm [4, 35], male sex [6, 9, 11, 18], age ≥60 years [7], no treatment with radiotherapy [36] and positive surgical margins [37].

etiology

Risk factors include exposure to sunlight and ultraviolet (UV) light. MCC seems to have a relationship with sun exposure, both by its anatomic predilection and geographic distribution. Miller and Rabkin reported a correlation of the UV B index and the incidence of MCC [3]. An association has been reported between MCC and other UV light-related skin cancers (squamous cell carcinoma, basal cell carcinoma) previous irradiation and exposure to radiant infrared heat [10, 38–43]. The development of MCC in non-sun-exposed regions of the body suggests that factors other than sunlight have been implicated in the pathogenesis of MCC. Lunder and Stern [44] reported a 100-fold increased incidence of MCC in patients treated with methoxsalen and UVA for psoriasis. Exposure to arsenic has also been implicated [45]. Immunosuppression and immunosuppression may represent additional risk factors for MCC, whose prevalence is unusually high in organ recipients compared with the general population [46, 47]. The risk of MCC in renal recipients has been estimated at 0.13/1000 person-years [48]. A high prevalence of second neoplasm occurring before, concurrent with or after the diagnosis of MCC (25%–28%) has recently been reported. These neoplasms include squamous cell carcinoma, hematological malignancies, breast cancer and ovarian cancer [43]. MCC has also been reported in patients with HIV infection and in those with chronic lymphocytic leukemia, suggesting that these diseases have an association with MCC. Engels et al. [49] reported that the relative risk of developing MCC in patients with HIV infection is approximately 13.4.

pathology

MCC involves the dermis and frequently extends into the subcutaneous fat. Sometimes, MCC involves the overlying epidermis [50]. The tumor consists of small blue, ovoid cells with hyper-chromatic nuclei, a very fine chromatine and minimal cytoplasm. Mitoses are frequent and the apoptotic index high. The triad of vesicular nuclei with small nucleoli, abundant mitosis and apoptosis is suggestive of MCC.

The most widely accepted origin of MCC is the Merkel cell [51], whose function is not clear. This clear, oval cell is located within or close to the basal layer of the epidermis and functions as a cutaneous mechanoreceptor [52]. The ultrastructural and immunohistochemical similarities between MCC and Merkel cells support the Merkel cell origin of MCC [53–55]. However, there is evidence that runs counter to this postulate: MCC and Merkel cells have different location (dermis and epidermis, respectively) and MCC does not express vasoactive intestinal peptides and metenkephalin specific to Merkel cells [56]. An intermediate consideration suggests that the origin of MCC is associated with an immature, totipotential stem cell that acquires neuroendocrine characteristics during malignant transformation [56, 57]. The same concept of precursor stem cells may explain the coexistence of MCC and squamous cell carcinoma of the skin [38].

Although MCC can usually be diagnosed histologically rather easily, it sometimes may be difficult using light microscopic findings due to its similarities with other small cell tumors. These include metastatic oat cell carcinoma, metastatic carcinoid tumor, neuroblastoma, and some types of melanoma, lymphoma and squamous cell carcinoma [11, 57]. MCC can be definitively diagnosed with hematoxylin–eosin and immunohistochemical staining, electron microscopy or both [15, 25]. Immunohistochemical staining can distinguish MCC from these tumors. MCC express both neuroendocrine (neuron-specific enolase, synaptophysin, chromogranin) and cytokeratin markers (cytokeratin 20, as a paraneuronal dot, CAM 5.2) and is negative for S100 and common leukocyte antigen. Epithelial membrane antigen and BEP-EP4 may also be expressed in MCC. Cytokeratin 7, which identifies bronchial small-cell carcinoma, is negative in MCC. In addition, a homeodomain-containing nuclear transcription factor expresses in bronchial small-cell carcinoma and is negative in MCC [58, 59]. On the contrary, neurofilament protein is commonly expressed in MCC and often not in bronchial small-cell carcinoma [60, 61]. CD 117 (KIT receptor) is also
present in 95% of MCC, but its expression does not correlate with more aggressive tumor [62].

Three histological subtypes of MCC have been reported: intermediate, small cell and trabecular, but these variants have no clinical relevance [63]. Intermediate variant is the most common seen subtype; the small-cell variant is histologically similar to other small-cell carcinomas and should be distinguished from the bronchial small-cell carcinomas.

**molecular biology of MCC**

Numerous chromosomal abnormalities have been reported in MCC, but the exact pathways of neuroendocrine differentiation are yet unclear. The most interesting chromosomal abnormality is the deletion of the short arm of chromosome 1 (1p36) [64, 65], which is also common in melanoma and neuroblastoma [66, 67]. These findings lead to arguments about the neurocrest origin of MCC [68]. Another abnormality is the loss of heterozygosity in chromosome 3p21, the same region that is also affected in small-cell lung cancer [69].

Several other abnormalities have been reported, including trisomy 1, trisomy 6, trisomy 11, trisomy 18 and deletion of chromosome 7 [70–73]. Loss of heterozygosity has also been reported in chromosomes 10q and 13 [74, 75]. The tumor suppressor gene p53 is also occasionally present in MCC, and the expression of mutant p53 may be associated with poor outcome [76]. P73 has been localized in 1p36.33 and, as in melanoma, is expressed infrequently [77, 78].

Recently, Leonard et al. [79] reported that MNF (Merkel nuclear factor) contains the POU-IV family member Brn-3c and that Brn-3c is expressed in normal Merkel cells. In addition, Brn-3c protein reactivity is restricted to a subset of MCC biopsies and is not seen in biopsies revealing adherent, variant cell lines lacking neuroendocrine markers. In mice POU-IV Brn-3 and the transcription factor ATOH1 are very important for the function of normal Merkel cells and for neuroendocrine differentiation [31]. The precise role of these abnormalities in the prognosis of MCC has to be determined.

**imaging**

After diagnosis, patients should be assessed by imaging techniques to define the exact extent of disease. Because MCC behaves like malignant melanoma, lymphoscintigraphy may be used to localize sentinel nodes, which may harbor micrometastases. Lymphoscintigraphy in combination with intra-operative lymphatic mapping allows accurate and selective sampling of sentinel nodes [80]. Distant metastases are present in some cases at presentation. The pattern of metastases is not specific for MCC and seems to mimic multifocal invasion by other small-cell carcinomas. Ultrasonography of soft tissue may show hypoechoic nodules arising from the dermis. CT scan may demonstrate regional lymph node involvement or systematic metastases in the lungs, liver, bones and other sites [81].

Invasion of CNS is rare but should not be overlooked. In such cases, it is best to perform MRI.

Distant metastases and locoregional recurrence may be evaluated with somatostatin receptor scintigraphy (SRS) based on the neuroendocrine characteristics of MCC [80]. SRS is helpful in pre- and post-therapeutic evaluation of MCC. Compared with CT scan and MRI, SRS is less affected by inflammation, edema and tissues at the surgical and irradiated site [80, 82]. However, SRS may be limited in evaluating metastases in liver, kidneys and spleen. The presence of somatostatin receptors has also been used therapeutically in MCC [83]. Guihera-Rovel et al. [84] reported a sensitivity of 78% and a specificity of 96% in 20 MCC patients assessed by SRS.

**treatment**

Treatment options will be discussed according to the disease stages. Because of the rarity of MCC, there are no prospective trials investigating surgery, RT or chemotherapy (CT).

**stage I**

For stage I disease the main treatment strategies include surgery and radiation therapy. In these cases the reported 5-year survival reached 64%. Controversies exist regarding the best excision margins in MCC, as there are no prospective, controlled studies dealing with this aspect. Margins 2–3 cm wide and 2 cm deep have been generally accepted [2, 11, 18, 32, 86–88]. In the older series [14, 32], the recommended margins were ≥3 cm. In the studies by O’Connor et al. [14] and by Yiangoukasawan et al. [32], margins ≥3 cm were associated with reduction in local recurrence. Updating results were reported based on 102 patients with MCC treated at Memorial Sloan Kettering Cancer Center [35]. After a median follow-up of 35 months, the overall 5-year disease-specific survival rate was 74%. Recurrence of disease occurred in 55 patients (55%), and the most common site of first recurrence was within the draining lymph nodes (n = 35). Elective lymph node dissection was the only independent predictor of improved relapse-free survival. However, in the study by Ott et al. [9] and in the study by Gillenwater et al. [89], 66 patients with MCC of the head and neck region, no difference in outcome (locoregional control and survival) was noted when the resection margins were >2 cm or <2 cm or the patients had an adequate RT or <1 cm, or 1–2 cm, or >2 cm, respectively. In contrast, in the latest study, a comparison of the patients who did (n = 26) and did not (n = 34) receive post-operative radiation therapy revealed a significant difference in local [3 (12%) versus 15 (44%), respectively; P <0.01] and regional [7 (27%) versus 29 (85%), respectively; P <0.01] recurrence rates. There was, however, no significant difference in the disease-specific survival between these groups (P = 0.30). Distant disease developed in 36% of all patients regardless of therapy [89].

Mohs micrographic surgery has been considered as the best method of wide clearance. However, no controlled clinical trials comparing this method with the traditional wide excision have shown its benefit. O’Connor et al. [90] evaluated the use of Mohs micrographic surgery for this aggressive neoplasm. Standard surgical excision for local disease was associated with
high rates of local persistence [13 of 41 (31.7%)] and regional metastasis [20 of 41 (48.8%)]. Only one of 12 (8.3%) Mohs-treated patients, with histologically confirmed clearance, had local persistence of disease. Regional metastasis developed in four of 12 cases (33.3%). Regional metastasis developed in none of the four patients treated with RT after Mohs surgery and in four of eight patients treated with Mohs surgery without post-operative RT. Boyer et al. [91] retrospectively conducted a study; the study group consisted of 45 patients with stage I MCC who were histologically and clinically free of disease after Mohs excision. Twenty patients subsequently received elective post-operative RT to the primary site and 25 patients had no adjuvant radiation therapy. One marginal recurrence (4%) and three in-transit metastases were observed in the Mohs surgery alone group, whereas none were observed in the Mohs surgery and RT group. The proportion of patients with these events was not significantly different between treatment groups. Overall survival, relapse-free survival and disease-free survival were not significantly different between treatment groups [91]. They concluded that adjuvant RT appears unessential to secure local control of primary MCC lesions completely excised with Mohs micrographic surgery.

MCC is a radiosensitive malignancy and adjuvant RT has been advocated for local and regional disease control [6]. Because of the high rate of local or regional relapse, RT has been used post-operatively, in an adjuvant basis in patients with MCC. However, most of the studies argued for the benefits of post-surgery RT [6, 33, 92–97]. Allen et al. [35] found that local recurrence occurred in approximately 12% of patients and was not more common in those who did not receive adjuvant RT after resection of the primary lesion. Adjuvant RT should be considered in patients with primary disease in whom wide surgical margins are unattainable or in those found to have pathologically close or involved margins after excision. In contrast, Wilder et al. [97] reported in a review that the administration of RT post-operatively to both the surgical bed and the draining lymph nodes improves locoregional control and may result in long-term disease-free survival when administered after the initial surgical resection. Similarly, Shaw et al. [18] in a review of 30 reports of MCC reported that after excision alone of the primary lesion, local recurrence occurred in 39% of patients and regional failure occurred in 46%. In contrast, patients treated by excision plus prophylactic treatment (adjuvant node dissection and/or adjuvant RT), experienced local recurrence in 26% and regional failure in 22%. Locoregional recurrence carried an ominous significance with 67% of patients subsequently dying of the disease. For patients who either presented with regional disease or later developed regional disease, the best outcome (44% survival with mean follow-up of 40 months) was obtained following treatment by therapeutic node dissection with or without RT. On the contrary, treatment of regional disease with RT alone was associated with only a 20% survival rate. In addition, Ott et al. [9] treated 31 patients with MCC of the head and neck region. Therapy included local excision with or without RT in 19 patients, local resection and lymphadenectomy with or without RT in eight patients, and RT alone in four patients with head and neck tumors. They concluded that locoregional recurrence correlates with inadequate margins and lack of RT, but remission is possible with multimodality therapy. Similarly, Meeuwen et al. [6] demonstrated the importance of surgery plus RT over surgery alone in preventing local recurrence of this highly malignant skin cancer. Medina-Franco et al. [98] reviewed 1024 cases with MCC and reported that adjuvant RT was associated with a reduced risk of local recurrence ($P < 0.00001$). RT has also been used alone and has been reported to achieve local control [92, 94, 99, 100]. The administered dose of RT ranges from 30 to 70 Gy, but the majority of patients received 45–50 Gy [31, 70].

Patients with MCC have at presentation 10%–30% regional lymph node involvement [11] and micrometastatic disease in prophylactic lymph node dissection has been found in 100% of patients [31]. Because the incidence of regional lymph node metastases is extremely high, ranging from 45% to 91% at diagnosis [11, 25, 26], elective nodal surgery with RT should be considered in patients with stage I disease. Controversy regarding the management of clinically negative lymph nodes has been eliminated with the use of sentinel lymph node mapping (SLN) for patients with MCC [15, 101, 102]. Approximately 25% of patients with MCC have metastatic disease in the SLN [15, 35]. Prophylactic lymph node dissection is not recommended as standard management [63, 87]. However, some investigators have recommended the prophylactic use of lymph node dissection for tumors at high risk for recurrence [87]. If metastatic disease is proved in SLN, management includes complete lymphadenectomy plus post-operative RT. Early removal of microscopic disease in regional lymph nodes detected by SLN biopsy may afford the patient a greater opportunity for cure than expectant management of the regional nodal basin, although this remains unproven [103]. Unfortunately, over half of the patients who undergo regional lymphadenectomy for clinically positive nodes will die of distant metastases [18, 32]. Lymphoscintigraphy and sentinel node biopsy have been proposed to overcome the problem of unpredictable lymphatic drainage and to minimize the need for node dissection [104, 105]. A meta-analysis of case series of 60 patients with Merkel cell carcinoma managed with sentinel lymph node biopsy was performed by Mehrany et al. [101]. Forty of 60 patients (67%) had a biopsy-negative sentinel lymph node; 97% of this group had no recurrence at 7.3 months median follow-up. Twenty patients (33%) had a biopsy-positive sentinel lymph node; 33% of this group experienced local, regional or systemic recurrence at 12 months median follow-up. Risk of recurrence or metastasis was 19-fold greater in biopsy-positive patients (odds ratio, 18.9; $P = 0.005$). None of 15 biopsy-positive patients who underwent therapeutic lymph node dissection experienced a regional recurrence. They concluded that sentinel lymph node positivity is strongly predictive of a high short-term risk of recurrence or metastasis in patients with MCC. Therapeutic lymph node dissection appears effective in preventing short-term regional nodal recurrence. The role of adjuvant CT in stage I MCC remains experimental. However, aggressive adjuvant treatment should be considered for patients with positive sentinel lymph nodes [101].

stage II

If stage II disease has been documented, management should include simultaneous excision of the primary site, regional
lymph node dissection and RT to the primary tumor and regional nodal site. Lymph node involvement is frequently bulky and the decision for operation should be based on the operability of the nodal mass, the patient’s performance status and the site of lymph node involvement [31]. RT at a dose of 50–60 Gy should be used for the regional nodal mass.

CT can be given in high-risk patients [106–109]. In a small series of 35 patients [86] no benefit from adjuvant CT was obtained. In contrast, Boyle et al. [7] reported a 40% (eight of 20) RR to CT, particularly CBDCA plus VP-16 given to patients with regional lymph node disease. They proposed that for such poor-prognosis tumors, further investigation of adjuvant RT and CT is warranted, as responsiveness of recurrent disease has been confirmed. In patients with recurrent or locally advanced disease and adequate performance status, Tai et al. [110] feel that chemoradiation (radiotherapy plus CAV-cyclophosphamide, doxorubicin or epirubicin, and vincristine or cisplatin and etoposide) may be considered as a treatment option.

stage III

Distant metastases are frequent at initial presentation [11, 32]. These lesions may be found incidentally at routine radiographic work-up or imagine evaluation for unrelated causes. The pattern of metastasis is not specific for MCC and mimics multifocal invasion by other small-cell carcinomas. However, organs most frequently affected are the liver, bone, lung, brain and skin. The prognosis of patients with stage III MCC is poor, with an average interval of 8 months between diagnosis and death [10]. Treatment consists of CT, palliative RT and possibly surgery. CT for MCC includes several regimens consisting of cyclophosphamide (CTX), doxorubicin (ADR), vincristine (VCR), 5-fluoruracil (5-FU), cisplatin (CDDP), carboplatin (CBDCA) and etoposide (VP-16) [10, 86, 106, 110, 111]. CT has only short-lived success in patients with MCC [10, 14].

RT can be given for palliation of bone and brain metastases or for palliation of cutaneous deposits that are bleeding or fungating. CT is usually reserved for those patients with generalized disease or advanced local or regional disease. Several investigators have reported favorable responses using a variety of regimens [110, 111]. Complete response rates of 20%–35% (median duration 6 months) and partial response rates of 23%–50% have been reported in patients with stage III disease [86, 110–112]. Voog et al. [111] reviewed 37 reports on the use of CT for 107 patients with MCC. The reported response rate was 60% for patients with locally advanced disease and 57% for those with metastatic disease. Cisplatin, ADR and 5-FU were the agents most commonly associated with a significant response. Cyclophosphamide was utilized in 56% of cases, ADR in 49% of cases and platinum derivatives in 25% of cases. Tai et al. [110] confirmed these results, reporting RR in 68% of patients with locally advanced disease and 59% in those with metastatic disease. Cyclophosphamide, ADR or epirubicin (EPI) and VCR appeared to be the most active agents. The reported RR was 75.7% (CR 35.1%). The combination of CDDP or CBDCA plus VP-16 had a RR of 60% (CR 36%). These responses did not differ significantly ($P = 0.19$). In our study [112] the RR was 83% (CR 33%), PR 50% for patients both with locally advanced and metastatic disease.

conclusions

MCC is a rare and aggressive neuroendocrine tumor of the skin. The optimal treatment for patients with MCC remains unclear. The best outcome is achieved with multidisciplinary management. Optimal management of patients with MCC consists of optimal surgery of primary tumor with adequate margins and post-operative RT to control local and regional disease. SLN mapping is essential in patients with clinically negative lymph nodes because it provides important prognostic information and allows selection of patients for additional nodal therapy. Patients with localized disease should be treated with conservative surgery followed by post-operative RT. The dose of post-operative RT ranges from 45 GY to 60 GY in 25–30 fractions. Patients with resectable nodal disease should be treated with regional node dissection followed by post-operative RT. Patients with fixed, unresectable nodal metastases should be treated with pre-operative CT plus RT followed by a nodal dissection. Because MCC has a propensity to develop hematogenous metastases and the responses to CT are high, adjuvant CT should be considered as part of the initial treatment. CT based on regimens for small-cell lung cancer resulted in tumor regression in up to 70% of cases with metastatic disease.

references


