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Review Article

Clinical features and management of Merkel Cell Carcinoma

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Abstract

Merkel cell carcinoma (MCC) is an aggressive dermal tumour of neuroendocrine origin. MCC is a rare tumour and all information pertaining to its behaviour, therapy and prognosis is based on retrospective reports. The two potentially curative treatment modalities are surgery and radiotherapy. It is a rare, highly malignant primary skin tumour, originally called "trabecular carcinoma" of the skin. MCC poses a challenge to the clinician because of its rarity and poor prognosis. The optimal therapy is customised and tailored for each individual patient with the appropriate use of operative resection and radiation therapy. This review covers reports from several authors regarding the rationale of using postoperative radiotherapy to the primary tumour and regional lymphatics. Although MCC is classified as a type of neuroendocrine carcinoma, it is less likely to be controlled by systemic chemotherapy. Management of primary lesion with clinically localised disease is wide excision with margin of at least 2 cm whenever possible. MCC is a radiosensitive tumour, adjuvant radiotherapy has been advocated in order to control local as well as regional disease Radiation induced toxicity should be considered and discussed with the patient. Adjuvant radiation to the nodal bed after complete lymphadenectomy in patients with metastatic disease is generally not recommended.

Introduction

Merkel cell carcinoma (MCC) is an aggressive dermal tumour of neuroendocrine origin. It is a rare, highly malignant primary skin tumour, originally called "trabecular carcinoma" of the skin. MCC poses a challenge to the clinician because of its rarity and poor prognosis.[1] It was first described by Toker in 1972.[2] He had observed that the tumour originates from the neuroendocrine cells of the basal epidermis of the skin. Merkel described the cell of the origin as epidermal, non-dendritic, non-kerotinocytic cell that he referred to as a tactile cell.[3] Electron microscopy and immunocytochemical studies are often required for accurate diagnosis.

Clinical Features: Although this carcinoma is usually found in elderly individuals, it can occur in young patients as well. Median age at presentation is approximately 67 years. The vast majority of patients affected by MCC are white. It has strong male predominance. Mostly MCC, occur on areas of the body exposed to sunlight.[4] Common sites of the tumour are head and neck (47-50%), extremities (40%) and trunk (8%).

The aetiology of MCC is not known. Sun exposure is considered as one of the risk factors as ultra violet exposure induced C to T mutation was found in some MMC cell lines.[5] The occurrence of MCC has also been reported in HIV infected patients together with other malignancies. Recent reports have shown an increased incidence in immunosuppressed transplant patients, in rheumatoid arthritis and in B cell malignancies.

The natural history of MCC shares many common features with melanoma like melanoma MCC is also a cutaneous malignancy of same embryonic origin. These two malignancies also show similar clinical features and behaviour e.g an early spread to nodal sites, high local recurrence rate and early metastasis.[6]

Yom et al[7] suggested that the differential diagnosis of Merkel cell carcinoma should be included in patients presenting with mucosal lesions of head and neck, especially if the tumor is sub-mucosal. MCC can also involve the tongue. Mucosal MCC is aggressive, and there is a high risk for local recurrence and regional and distant metastasis.[7]

Diagnostic evaluation: Histologically the tumour consists of sheets of small round blue cells, an appearance that is similar to melanoma and metastatic small cell carcinoma. Immunohistochemical stains may be used to determine whether the primary tumour is indeed a primary MCC of the skin or cutaneous metastases from a visceral small cell carcinoma. MCC has immunohistochemical features of both neuroendocrine and epithelial cells. It is usually positive for cytokeratin, CK20 (unlike melanoma and metastatic squamous cell carcinoma) and is usually negative for S100 and thyroid transcription factor 1(TTF-1), a newly described nuclear protein that appears to be specific for small cell carcinoma of pulmonary origin.[8]

A report published in Anticancer Research in June 2006 has evaluated the role of cell cycle-regulatory proteins(p53/p21/p27) in Merkel Cell Carcinoma's pathogenesis and prognosis. Twenty-four primary MCC specimens with corresponding clinical data were analysed by immunohistochemistry for p21, p27 and p53 antibodies.

The staining was evaluated semi-quantitatively and the results were analysed. p53 was negative in 80% and p21 in 71% of the samples. Positive staining for p27 was evident in 92% of the samples. However, the expression of these antibodies did not correlate with the outcome of the patient.

The proportion of p53- and p21-negative samples seems to indicate that correction processes after DNA damage are not activated during MCC pathogenesis, a supposition that is supported by the aggressive nature of this tumour. It was concluded that the above mentioned three cell cycle regulators cannot serve as prognostic markers for survival.[9]

Under the microscope most of the MCC specimens show a clear Grenz zone separating the epidermis from the tumour.The immunohistochemistry of MCC exhibits positive staining to neurofilament,cytokeratin,neuron specific enolase and epithelial membrane antigen.[10]

Staging: Patient with MCC can be staged according to the American Joint Committee on Cancer (AJCC) staging system for skin cancer. Alternatively, a relatively simple system was proposed by Yiengpruksawan et al.[11] which can be used for stage grouping:

StageI : patients with localized disease; those with tumour of less than 2 cm are considered stage 1A, whereas those with tumour of 2 cm or more are considered as stage 1B.

Stage II, with regional lymph node metastasis

Stage III; with distant metastasis.

Yiengpruksawan and colleagues have reported that at the time of first consultation 70% to 80% of patients with MCC have stage I, 10% to30%have stage II and 15 to 4% have stage III disease.[11]

Treatment: MCC is a rare tumour and all information pertaining to its behaviour, therapy and prognosis is based on retrospective reports. The two potentially curative treatment modalities are surgery and radiotherapy. The optimal therapy is individualised in any given patient with the appropriate use of operative resection and radiation therapy. Several authors reported that postoperative radiotherapy to the primary tumour and regional lymphatic significantly improves local control and disease free survival,[12] The mainstay of treatment is wide local excision of tumour with reconstructive surgery.[13]

Management of primary lesion with clinically localised disease is wide excision with a margin of at least 2 cm whenever possible. The excision should include the skin and subcutaneous tissue. Resection of the underlying fascia is also performed when the tumour is close to it. Excision margins of less than 3cm are associated with high incidence of local failures.[11] Due to high incidence of nodal metastasis, prophylactic lymphadenectomy is also suggested in some reports, alternatively sentinel node biopsy can be considered as an appropriate procedure in clinically node negative patient. Approximately 25% of patients are found to have metastatic disease in the sentinel node biopsy. Early removal of microscopic disease detected by this diagnostic approach may offer the patient a greater opportunity for cure.[14] It is often difficult or impossible to excise MCC of the head and neck or distal extremity with a wide margin. Adjuvant radiotherapy can be considered in these cases. If the primary cancer is to be treated with radiotherapy alone, the regional lymphatics may be electively irradiated. Patient who present with fixed, unresectable nodal metastasis are treated with preoperative radiotherapy followed by salvage surgery of the primary site with a possible nodal dissection.

MCC is a radiosensitive tumour, adjuvant radiotherapy has been advocated in order to control local as well as regional disease.[12] Radiation induced toxicity should be considered and discussed with the patient. Adjuvant radiation to the nodal bed after complete lymphadenectomy in patients with metastatic disease is generally not recommented. Regional recurrence is uncommon after a complete lymphadenectomy is performed in patients who had positive sentinel node biopsy.[14] On the other hand in patients with clinically proven regional disease adjuvant radiation treatment improves regional control.

There is no established dose response curve for the MCC. It is quite likely that its response to radiation is similar to that observed in squamous cell carcinoma. Therefore, the dose fractionation schedule for patients with negative surgical margin is of the order of 60 Gray in 30 fractions over 6 weeks or equivalent.[15]

Systemic chemotherapy is recommended in patients with regional or systemic metastasis as a palliative measure. It gives 50% to 60% palliative response rate which is found to be more evident in patients with regional disease and less for visceral metastases. The use of various chemotherapeutic agents, both single and in combination, are reported in the literature. Agents like cyclophosphamide, doxorubicine, vincristine, etoposide, cisplatin, carboplatin, octreotide and dacarbazine have shown some palliative benefits.[16] The option of systemic chemotherapy should be offered to patients who present with nodal or metastatic disease.[17]

A metanalysis concluded that surgery plus adjuvant irradiation was associated with significantly lower rates of local and regional recurrence of MCC than surgery alone. Prospective investigation is needed to clarify the presence

of a survival benefit from combination therapy.[1]

Swann and Yoon have done a review of MCC which is published in the Seminars of Oncology in February 2007. They have drawn some pertinent conclusions on the prognosis and management of MCC. The prognosis of MCC is variable. Natural history of localized disease is indolent and these tumours are well controlled with local excision alone. On the other side of spectrum , majority of tumours behave aggressively and have a tendency for locoregional recurrence and distant metastases. In locally advanced and metastatic disease the option of systemic chemotherapy with regimens similar to those which are used in the treatment of small cell carcinoma of the lung, may be considered in adjuvant setting following surgery.[18]

MCC is characterized by a high incidence of local and regional recurrence. Long term survival with low incidence of recurrence is reported in patients with early stage of tumour. Most recurrences occur in the first 24 months and frequent follow up during this period is recommended. Patients who develop a local recurrence after primary excision (regardless of site) should undergo re-excision, if possible, and adjuvant radiotherapy should be considered if not previously given. The long survival can be achieved after the treatment of loco regional recurrence. Voog and colleagues have reported that patients with loco-regional relapse and distant metastasis had 2 year survival rate of 35% and 17% respectively, versus 86% and 100% respectively for those who do not have these two forms of recurrences. The median overall survival after starting chemotherapy was 9 months for patients with distant metastasis and 24 months for patients with loco regional disease.[16] The role of immunotherapy is not fully defined. Immunotherapeutic agents such as alpha- interferon or intralesional application of tumour necrosis factor-alpha were shown to have some effects in some patients.[19,20]

Sandel HD et al[21] compared the clinical and histopathological criteria including tumour size and depth of invasion with clinical outcomes in MCC patients. Disease-free survival rates were found to be 52%, 39%, and 9% at 1, 2, and 5 years, respectively. The average disease-free interval was 18.4 months (range, 1-80 months). Overall recurrence was found in 60.7% of patients with local recurrence occurring in 18.1%, regional recurrence 40.9%, and distant recurrence 47.8%. However, there was a trend toward increased local and regional recurrence rates when comparing size and depth and in specimens with positive tumor margins.[21]

These outcomes are consistent with those reported in recent literature and further characterize the unpredictable nature of this disease. An aggressive approach should be taken, including wide local excision with negative tumor margins and lymph node dissection.

Ortin Parez et al[22] have reported eight cases of MCC who underwent sentinel node biopsy. All sentinel nodes were successfully harvested. Three patients (37.5%) showed metastatic involvement and they were subjected to regional lymphadenectomy.This report published in the European Journal of Surgical Oncology in February 2007 suggested that sentinel node biopsy appears to be a reliable staging technique which can be considered in the surgical management of MCC.[22]

A retrospective review was published in the Journal of Surgical Oncology in March 2007. The review of 38 consecutive patients with surgically treated extremity MCC was presented. Surgical techniques of Wide local excision and Mohs' surgery was compared. No difference in local recurrence was found between the two procedures. A reduced local recurrence rate was observed in patients who were treated by adjuvant radiotherapy with a hazard ratio of 0.29 (95% Confidence Interval [0.10, 0.85]).It has no impact on overall survival.This retrospective review further supports the rationale of using adjuvant radiation therapy in improving locoregional tumour control in MCC patients.[23]

References

1. Lewis KG, Weinstock MA, Weaver AL, Otley CC.Adjuvant local irradiation for Merkel cell carcinoma. Arch Dermatology. 2006 142:693-700.
2. Toker C. Trabecular carcinoma of skin. Arch Dermatol 1972. 105; 107-10.
3. Goessling W, McKee PH, Mayer RJ. Merkel cell carcinoma. J Clin Oncol 2002; 20: 588-98.
4. Akhtar S, Oza KK, Wright J: Merkel cell carcinoma ; report of 10 cases and review of the literature. J Am Acad Dermotol 2000;43: 755-67.
5. Van Gele M,Kaghad M,Leonard JH,Van Roy N,Naeyaert JM,Geerts ML,et al.Mutation analysis of P73 and TP53 in Merkel cell carcinoma. Br J Cancer 2000;82: 823-6.
6. Price P, Sikora K. Treatment of Cancer,4th Edition. Arnold Publishers London 2002; pp 1213-9.
7. Yom SS, Rosenthal DI, El-Naggar AK, Kies MS, Hessel AC. Merkel cell carcinoma of the tongue and head and neck oral mucosal sites. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006;101:761-8.
8. Leech SN, Kolar AJ, Barrett PD,Sinclair SA,Leonard N. Merkel cell carcinoma can be distinguished from metastatic small cell carcinoma using antibodies to cytokeratin 20 and TTF-1. J Clin Pathol 2001;54;727-9.
9. Koljonen V, Tukiainen E, Haglund C, Bohling T. Cell cycle control by p21, p27 and p53 in Merkel cell carcinoma.Anticancer Res 2006;26:2209-12.
10. Tope WD, Sangueza OP. Merkel cell carcinoma. Histopathology, immunocyto chemistry and cytogenetic analysis. J Dermatol Surg Oncol 1994;20:653-4.
11. Yiengpruksawan A, Coit DG, Thaler HT, Urmacher C, Knapper WK . Merkel cell carcinoma. Prognosis and management. Arch Surg 1991; 126: 1514-9.
12. Meeuwissen JA, Bourne RG, Kearsley JH. The importance of postoperative radiation therapy in the treatment of Merkel cell carcinoma. Int J Radiat Oncol Biol Phys 1995;31: 325-31.
13. Clifford KS, Parez CA,Brady LW.Radiation Oncology,management decisions.2nd Edition 2001,Lippincot Williams & Wilkins Publishers, Philadelphia, Chapter 13 pp 116.
14. Mehrany K, Otley CC, Weenig RH, Phillips PK, Roenigk RK, Nguyen TH. A metanalysis of the prognostic significance of SLN status in Merkel cell carcinoma. Dermatol Surg 2002;28;113-7.
15. Nathu RM, Mendenhall WM, Persons JT. Merkel cell carcinoma of the skin. Radiat Oncol Investig 1998;6:233-9.

16. Voog E, Biron P, Martin JP, BlayJY. Chemotherapy for patient with locally advanced or metastatic Merkel cell carcinoma. Cancer 1999; 85:2589-95.
17. Solan MJ, Brady LW, Binnick SA in Parez CA, Brady LW editors, Principles & Practice of Radiation Oncology,3rd Edition; Philadelphia; Lippincot Raven Publishers; pp 723.
18. Swann MH, Yoon J. Merkel cell carcinoma .Semin Oncol. 2007; 34:51-6.
19. Durand JM., Weiller C, Richard MA, Portal I, Mongin M. Treatment of Merkel cell tumor with interferon-Alpha-20. Br J Dermatol 1991;124:509.
20. Ito Y, Kawamura K, Miura T, Ueda K, Onodera H, Takahashi H . Merkel cell carcinoma. A successful treatment with tumor necrosis factor. Arch Dermatol 1989; 125:1093-5.
21. Sandel HD, Day T, Richardson MS, Scarlett M, Gutman KA. Merkel cell carcinoma: does tumor size or depth of invasion correlate with recurrence, metastasis, or patient survival? Laryngoscope. 2006;116:791-5.
22. Ortin-Perez J, van Rijk MC, Valdes-Olmos RA, Vidal-Sicart S, Nieweg OE, Vilalta A et al. Pons F. Lymphatic mapping and sentinel node biopsy in Merkel's cell carcinoma. Eur J Surg Oncol 2007;33:119-22.
23. Senchenkov A, Barnes SA, Moran SL. Predictors of survival and recurrence in the surgical treatment of merkel cell carcinoma of the extremities. J Surg Oncol 2007;95:229-34.