Review

Prognostic biomarkers, pathogenic studies and treatment of Merkel Cell Carcinoma

Umair Ali Khan Saddozai¹, Fengling Wang¹, Zhang Lu¹, Longxiang Xie¹, Zhongyi Yan¹, Saadullah Khattak¹, Muhammad Usman Akbar², Muhammad Badar², Wan Zhu³, Xinying Ji^{1,*}, Xiangqian Guo^{1,*}

¹Department of Preventive Medicine, Institute of Biomedical Informatics, Cell Signal Transduction Laboratory, Bioinformatics Center, School of Basic Medical Sciences, Henan University, Kaifeng 475004, China; ²Gomal Center of Biochemistry and Biotechnology, Gomal University, Dera Ismail Khan, Pakistan; ³Department of Anesthesia, Stanford University, 300 Pasteur Drive, Stanford, CA 94305, USA

*Corresponding author: Xiangqian Guo, E-mail: xqguo@henu.edu.cn; Xinying Ji, E-mail: 10190096@vip.henu.edu.cn

Received May 28, 2019; Accepted August 17, 2019

Merkel cell carcinoma (MCC) is a rare type of skin cancer of neuroendocrine origin. MCC found mostly in light-skinned peoples. In the past decades incidence ratio of MCC have been significantly increased. Numbers of different risk factor has been identified for MCC such as ultraviolet light exposure, advance and immunosuppression. Furthermore newly identified Polyomavirus is also interestingly found in large number of Merkel cell carcinoma patients. This paper will review the MCC evaluation, behavior, tumor size, stages, involvement of virus, treatment, prognostic biomarker and clinical aspects.

Key Words: Merkel cell carcinoma; Skin cancer; Merkel cell polyomavirus; Molecular Aspects

INTRODUCTION

Merkel cell carcinoma (MCC) was defined for the first time in 1972 by Cyril Tokar,¹ it is reported to be an uncommon neuroendocrine and cutaneous malignancy originating from sweat glands. It is also known as a (neuro) endocrine most cancers of the pores and skin or small-cellular carcinoma of the skin. Merkel cells are thought to arise from the neural crest and are believed to be the number one neural cells discovered as single cells inside the basal layer of the epidermis of the tactile hair disc of Pinkus inside the skin of mammals. Merkel cells are ideal for playing a role as mechanoreceptors and endocrine cells in skin sensory system.¹⁻⁵ Not only being a rare malignancy, but MCC is also an aggressive scientific course. About 66% of patients have local disease, 27% have nodal involvement and 7% have distant metastasis. The immunocompromised, aged people having hematological neoplasms and those who suffered from the cutaneous tumors in the past are at high risk of MCC. There is variation in the incidence ratio of MCC across the different regions of the world.

Epidemiology

Little is understood concerning the medical specialty of MCC. MCC may be a rare cutaneous tumor.^{6,7} Between 1995 and 2002, 0.13 per 100,000 incidences were reported by the surveillance of Rare Cancer in Europe (RARECARE) database.^{8,9} The incidence

rate was recorded as 1.6 per 100,000 individuals per annum in Australian state from 2006-2010¹⁰ and 0.3 per 100,000 individuals in Sweden in 2012.¹¹ The median diagnosis age is 75-80 years.^{10,11} It is the cancer of neoplasm of elderly people with estimation of 470 new cases within the U.S per year. This incidence figure compares with thirty-one thousand new cases of skin cancer annually. The age-adjusted incidence of MCC in U.S was found to be 0.24 per 100,000 every year.¹²

Clinical issues

Clinical symptoms of MCC are difficult to detect in the early stages.^{13,14} Clinical presentation of MCC can be variable. Most tumors appear as firm, red to purple, nontender papules or

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How to cite this article: Saddozai UAK, Wang FL, Lu Z, Xie LX, Yan ZY, Khattak S, Akbar MU, Badar M, Zhu W, Ji XY, Guo XQ. Prognostic biomarkers, pathogenic studies and treatment of Merkel Cell Carcinoma. *J ADV HEALTH* 2019; 1(3): 221-226.

nodules.⁸ Growth is fast and usually dome-shaped.^{14,15} MCC is mostly found on the skin of sun-exposed persons and has been reported on the head, neck, arms, legs, trunk, back, buttock and upper extremities.¹⁴⁻¹⁷ The head and neck area accounts for 48% of all MCC cases whereas non-sun-exposed areas are less regularly affected. Mucosal sites for example (larynx, nasal cavity, pharynx, mouth) account for 5% of primary MCCs. Tumour length may range between 2 to 2 hundred mm. However, it is found most commonly in much less than 20 mm. Merkel cell carcinoma has also been suggested to have an effect on the vulva and penis.⁸ Most affected persons are older than 60 years of age. Five percent of the cases are recognized earlier than the age of fifty.^{13,14} MCC generally observed in the first 3 years following diagnosis.^{16,18,19} Metastasis usually takes place in draining lymph node basin and subsequently expands to other parts of the body.^{13,16,20} A study conducted in 2011 suggested that good enough surgical elimination and selected adjuvant radiotherapy (RT) may reduce the neighborhood recurrence chances. However, sufferers with clinically high-quality lymph nodes have an excessive rate of recurrence in the shape of remote disorder.²¹

Merkel cell polyomavirus

MCPyV belongs to the family of Polyomaviridae³⁶. Dr Chang and team in their recent studies recognized a unique polyomavirus and introduced it into the order of MCC's genome. Out of ten samples, eight were found to be positive (infected with virus) and further studies confirmed the results. The detection frequency of Merkel cell polyomavirus through polymerase chain reaction was as little as 24% found in Australian patients and up to 85% in European and North American patients.²²⁻²⁵ Different research strategies are under process to define the virus's role in tumour. There is the latest observation that MCV-positive tumor cells undergo choice for mutations truncating the product of the large T antigen, thereby stopping virus replication. This proposes that MCV is not a "passenger virus".²⁶

Immune Response

The immune response is a process in tumor progression and is usually centered on the concept of persistent antigen expression as a means of immune down-regulation. Dunn *et al.*²⁷ suggested that cancer cells must interact through three consecutive phases with the host immune system (immune-editing hypothesis). In the elimination phase, the host immune system is able to recognize and destroy newly transformed cells through both the innate and adaptive immune systems. The second equilibrium phase allows the tumor to remain dormant and growth remains stagnant. Lastly, in escape phase, the tumor is able to escape host immune response. Host immune responses are an important part of MCC's progression and prognosis. Some patients with anti-MCPyV antibodies at higher concentrations (>10,000) are found to be more resistant towards progression of MCC and have good survival rate than the patients with low antibody concentrations (<10,000). Antibody concentration against the LT antigen may become potential MCC biomarkers in the future. Rising LT antigen titers have shown to correlate with disease progression and falling titers correlate with successful treatment.²⁸ Sihto *et al.* (2012) suggested the better prognosis from high intratumoral infiltration is not specific to MCPyV-positive MCC; however, it

does highlight an important aspect of tumor evasion taking place in the process by which cell surface antigens are known as Major Histocompatibility Complex (MHC) class I antigens are suppressed, allowing presentation of tumor intracellular peptides to CD8+ T lymphocytes.^{28,29} The upregulation of this specific immune response can become major pathway of future MCC treatments.

Molecular Aspects

Chromosomal abnormalities have been clearly defined in MCC. The most important of which is the loss on the short arm of chromosome 1 (1p36)³⁰⁻³³ that is also found in neuroblastoma pathogenesis³⁴ and melanoma,³⁵ suggesting that gene of tumor suppressor may be confined here. The *p73* has been found to localize 1p36^{36,37} but the latest study found mutations of the *p73* gene in one out of 10 sufferers with MCC,³⁸ which were much like the infrequent mutations of *p73* in cancer.³⁹ The tumor-suppressing gene (*p53*) is thought to express temporarily in MCC. Whereas mutant *p53* protein was found in 6 out of 9 patients with poor clinical outcomes as compared to 0 out of 10 patients with more favorable outcomes.⁴⁰ Every other critical abnormality may be reported as a lack of heterozygosity in chromosome 3p21^{41,42} but the same region is also affected in more than 90% of patients suffering from small-cell lung cancers. Newly postulated tumor suppressors gene (Ras association domain family 1 RASSF1A) belongs to the origin of neuroendocrine cells,^{43,44} which also indicates histological parts of small blue cells and early metastasize tendency. Lots of other different chromosomal abnormalities are also defined in MCC including trisomy 1, trisomy 6, trisomy 11, trisomy 18⁴⁵⁻⁴⁹ and deletion of chromosome 7.⁴⁶ The loss of heterozygosity is also found in chromosome 10q (50) and chromosome 13. According to reports, a common deletion of the retinoblastoma gene RB1 was found in one study.^{48,51,52} Moreover, various studies demonstrated the involvement of oncogenes or tumor suppressing genes in MCC pathogenesis. However, too little is known related to the prognostic value of reported abnormalities and no significant applicants have been found so far.

Prognosis and staging

Due to the aggressive nature of MCC, MCC patients have dismal outcomes based on historical data in small case series.¹³ However, MCC is not uniformly lethal.¹⁸ Most patients with MCC (70% to 80%) present localized disease, 10% to 30% have regional lymph node involvement, whereas 1% to 7% have distant metastases at the time of initial presentation.⁵³⁻⁵⁶ It is found that five-year survival rate for patients treated with local metastasis to regional lymph node ranges from 26% to 40%. But the 5 year survival rate of the patient with distant metastasis is 18%.^{8,12} However, overall survival rate of MCC patients ranges from 30% to 75%.¹³ Therefore Consensus staging system with four main stages of the cancer was introduced in 2010 by the American Joint Committee on Cancer (AJCC). Which based on tumor size, nodal involvement and the presence of distant metastasis^{57,58} SLNB (sentinel lymph node biopsy) is recommended for accurate staging. Similarly in 2016 a new advanced staging system was developed which separates groups of clinical and pathological stages. This reflects more precisely the difference in patient outcomes observed for these two methods of staging.⁵⁹

Biomarkers

Platelet-derived growth factor (PDGF) receptor, c-kit (CD117) and phosphoinositide 3-kinase (PI3K) are often overexpressed in MCC tumors, which may be linked to a worse prognosis for patients with MCC.⁶⁰⁻⁶² Although the analysis of tumor specimens with PI3K mutations suggests a more aggressive tumor pathology, an association between PI3K mutation status and patient survival has not yet been established.⁶¹ Several other biomarkers including PD-L1, p63, vascular endothelial growth factor receptor (VEGFR), Ki-67, CD34, Ep-CAM, nuclear factor kappa B, sonic hedgehog pathway proteins and matrix metalloproteinase have been suggested to predict disease outcomes in patients with MCC.⁶³⁻⁷⁰ However, comprehensive data to assign any specific biomarker to prognostic associations is still unavailable.

Quality of life

Almost all patients diagnosed with MCC have a similar quality of life. Generally, the patients are elder and suffer from other medical comorbidities. Patients above 75 years of age lack potential to tolerate multi-modal treatment.⁷¹ Such multi-modal treatments include variety of therapeutic strategies such as radiotherapy, locoregional surgery, systemic cytotoxic and focused or immune remedy. Therefore, an onco-geriatric assessment is required in selected patients before determining a control path. It has become very important to minimize the adverse effects associated with therapies. Acute toxicity arising from side effects can be fatal and have long term repercussions and patients' health. As MCC is a rare carcinoma, there are no valid MCC-particular quality-of-life measurement instruments and dermatology-specific instruments have not been validated for patients with MCC.

Further to the impact of receiving a prognosis of this aggressive cutaneous malignancy, treatment-associated toxicity could have a prime impact on patient's lifestyles. Thus, with old age patients having couple of comorbidities, various rapid-appearing and easy-to-use interventions (frequently radiotherapy alone) might be taken into consideration. The usage of systemic cytotoxic treatments in MCC management remains controversial with likely concerns in elderly sufferers. Inside the palliative placing, responses are frequently short-lived, and patient's quality of existence is more affected by treatment than by means of the disease. Application of chemotherapy in old age patients having superior-level MCC becomes difficult to complete the planned chemotherapy direction.⁷² However, improved efficacy and less toxicity of inhibitors make them a better option to use on this population.⁷³ The adverse effects of treatment on the lifestyles of patients cannot be underestimated as treatment-related toxicity is the priority of any management course and the goal of future research.

Treatment of MCC

Surgical excision is the strength of treatment for MCC patients.^{18,74,75} For the treatment with Mohs micrographic surgery or local excision the Current National Comprehensive Cancer Network guidelines recommend a margin of 1-2 cm. Patients undergoing wide local excision also required the compulsory intraoperative sentinel lymph node biopsy. Similarly preoperative sentinel lymph node biopsy is needed for patients undergoing Mohs micrographic surgery because of change in lymphatic

drainage which could affect lymphoscintigraphy.⁸ The effect of radiation therapy also plays an important role against MCC due to sensitivity.^{74,76,77} For MCC, patient's radiation may be used as adjuvant or primary therapy, whereas non-surgical candidate uses reserved radiation as primary therapy.

No difference has been found between the outcome of a small group of patients treated with radiation alone and patients who underwent surgery and radiation to the tumor bed.⁸ There is a trendy consensus that radiation treatment is advantageous for recurrent tumors. Chemotherapy is a good option as a pain killer therapy for stage IV cancer patients but only two-third of tumors respond to chemotherapy and the disease often recurs after few months. Current guidelines suggest that a small group of patients may not require adjuvant therapy following adequate resection of some small tumors and that the clinical observation may be appropriate.^{8,12} Chemotherapy may play a palliative role in patients with metastatic MCC. MCC is chemo-sensitive but with a high recurrence rate.⁸ The immune system plays an important role in disease prognosis and having an intact immune system is a plus point in the prevention of disease progression.

Future Treatments of MCC

Upregulation of immune response and viral etiology of the most tumor would be the focus for the future treatments of MCC, which may help in interfering with viral oncoproteins and in stimulating different immune responses against tumor cells.²⁸ Interestingly, in some tumors, MCPyV large T antigen was found to be overexpressed and may serve as definite target for new therapy.^{78,79}

LT antigen encoding key cycle surviving protein may be an exciting marker given its implication in many different cancers.⁸⁰ Other prospective non-viral molecular objectives are antigens containing the oncoprotein H1P1 that interacts with c-KIT. Specific immune-stimulatory cytokines that may be used to upregulate the immune response towards the tumoral cells may include IL-2, IL-12, IL-15, or IL-21. Therapeutic agents may become the main focus of study in the future to set a target immune exhaustion phenomenon related to tumorigenesis containing ipilimumab (cytotoxic T lymphocyte antigen 4 receptor-blocking agent). It also needs a focus on programmed cell death 1 ligand 1 and programmed cell death 1 (PD-1/PD-L1).²⁸ Tumour of neuroendocrine containing MCC tends to express vascular and highly vascular endothelial growth factors, and platelet of growth factors, which may become other possible therapeutic targets. According to reports, 95% patients of MCC are CD56+, and present clinical trials suggest a promising therapeutic response with anti-CD56 monoclonal antibody.¹²

CONCLUSION

Great development has been made in our expertise of MCC tumor biology and immunology. The occurrence of MCC is increasing due to the advancing age of the populace, a higher prevalence of negative solar exposure, and an increase in the number of immune-compromised people. Merkel cell polyomavirus keeps importance regarding the etiology of MCC. However, the local or regional treatments have their value and they remain standard of care. Adjuvant radiotherapy or radiotherapy on its own has been found to be affordable therapeutic options. Such progressed understanding is gradually and effectively translated into the medical situation. For this reason, the mortality charge and diagnosis of patients

imparting with advanced ailment have remained exceedingly unchanged. The latest advances within the development of properly tolerated immunotherapy sellers will have the capacity to offer effective remedy alternatives for sufferers with advanced or recurrent MCC in near future.

Conflict of interest

We all authors declare that we have no conflicts of interest for this article.

Funding

This work was supported by the National Natural Science Foundation of China (No. 81602362 to XG), the program for Science and Technology Development in Henan Province (No.162102310391 to XG), the program for Young Key Teacher of Henan Province (No.2016GGJS-214 to XG), the supporting grants of Henan University (No.2015YBZR048 to XG; No.B2015151 to XG), the program for Innovative Talents of Science and Technology in Henan Province (No. 18HASTIT048 to XG), and Yellow River Scholar Program (No.H2016012 to XG). The funding bodies were not involved in the study design, data collection, analysis and interpretation of data, or in writing of this manuscript.

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