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Merkel cell carcinoma: literature review

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Merkel cell carcinoma (MCC) was given a such name after the German histopathologist Friedrich Merkel, who first in 1875, described the Merkel cells, as small round or oval basophilic cells located at the end of nerve axons and within the basal layer of the epidermis. The current agreement about the function of Merkel cells they are associated with the nerve terminals acting as mechanoreceptors. MCC is a clinically aggressive uncommon, cutaneous neuroendocrine neoplastic tumour with a high mortality rate. Clinically may be presented as a painless, rapidly growing, dome-shaped red or purplish nodule. Usually in a sun-exposed area of the head and neck or upper limbs. Tremendous effort has been done in the last few years for a better understanding of the pathogenesis behind the MCC and the discovery of the Merkel cell polyomavirus suggests another clue to its pathogenesis. The expression of both epithelial and neuroendocrine immunohistochemical markers in the malignant cells, gives the tumour a unique feature that helps differentiate this neoplasm from other entities.

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Key words: Merkel cell carcinoma, trabecular carcinoma, Toker tumour, polyomavirus

Introduction

Merkel cell carcinoma (MCC) is a highly aggressive neuroendocrine carcinoma of the skin. In spite it is a rare tumour, its incidence is increasing. It is known to have high rates of recurrence and distant metastasis. MCC is a frequently lethal skin cancer with a higher mortality (33%) than melanoma (15%) [1]. This cancer is known with rapid progression course and poor prognosis. British National Cancer Intelligence Network 10 year incidence rate for rare skin cancer across English Cancer Registries (1999–2008) Report revealed evidence for increasing standardised incidence rates of Merkel cell carcinoma (0.1 to 0.2 per 100,000 population). Risk factors include, polyomavirus, UV light, immunosuppression and presence of other cancers as lymphomas.

Historical background

Freidrich Sigmund Merkel, a German histopathologist, first described the Merkel cells in 1875 using animal modules. They are clear-staining cells at the dermo-epidermal junction were near myelinated nerve fibers, they acted as mechanoreceptors, other Merkel cells that have no contact with nerve terminals appear to have an endocrine function [2]. Intriguingly, three years later, the term Merkel cell was born by a young anatomist Robert Bonnet who later worked with Dr. Merkel [3]. The first human cases was first reported in 1972 by Toker, who was born in South Africa and worked as a Professor of Pathology at University of Maryland School of Medicine in Baltimore, USA. He used the term "trabecular carcinoma" of the skin to describe a poorly

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differentiated carcinoma of the dermis and subcutaneous tissue [4, 5], this is why some papers called this disease as Toker Tumour.

Epidemiology, risk factors & pathogenesis

MCC is a frequently lethal skin cancer with a higher mortality (33%) than melanoma (15%) [1]. This cancer is known with rapid progression course and poor prognosis. British National Cancer Intelligence Network 10 year incidence rate for rare skin cancer across English Cancer Registries (1999–2008) Report revealed evidence for increasing standardised incidence rates of Merkel cell carcinoma (0.1 to 0.2 per 100,000 population). Risk factors include, polyomavirus, UV light, immunosuppression and presence of other cancers as lymphomas.

The increased incidence of the disease could be due to actual incidence increase. Other factors are blamed as growing aged population, increased sun exposure (Tropical Holiday Factor), tanning salons, advancement in immunohistochemical diagnostic techniques together with better registration facilities. MCC occurs more often among elderly fare skin patients with somewhat more commonly in males [6]. Most common on sun-exposed areas or artificial light [4, 10, 11]. Predominantly occurred in head and neck area (more than 50%) followed by limbs (40%). The rest 10% reported in the trunk [4]. Non-sun exposed area MCC also has been reported as vulva [12], tongue [13] and gluteal area [14]. In the year 2008, a team from University of Pittsburgh, USA, came with new break through related to the pathogenesis of MCC. It is related to Merkel cell polyomavirus (MCV or MCPyV), reports mentioned that it is present in 80% of cases. It is a small novel polyomavirus with a genome consisting of double-stranded DNA. Thus, MCV may be a contributing factor in the pathogenesis of MCC [6, 15, 16]. The MCPyV large T antigen contains MCC tumor-specific mutations that withdraw its replication capability, however perpetuate its oncogenic functions, and the small t antigen encourages an environment propitious for carcinogenesis [17, 18]. Immuno-suppression increases the relative risk of MCC especially with HIV, solid-organ transplant patients as well as autoimmune diseases [19–22]. Also patients with lymphoproliferative disorders as chronic lymphocytic leukaemia (CLL) have an increased risk of MCC [23].Other cancers associated with MCC are skin squamous cell carcinoma, basal cell carcinoma, malignant melanoma, Hodgkin lymphoma, Non-Hodgkin Lymphoma [24].

There are reports about primary MCC arises in the breast skin [25], however there is a case of coexistence of MCC with a breast cancer [26]. The reported observations support the existence of shared risk factors for MCC and other cancers. It is reported that the Merkel cell polyomavirus has a potential oncogenic effect [1, 15, 16], is it possible that, this virus also related to the other cancers. This is a need for more research to be done in this field.

Clinical picture

Clinical picture could be a reddish blue, firm, non-tender, nodular mass that has grown rapidly over a few weeks or even for months, this may ulcerate. They metastasise to lymph nodes (55%), liver, lung and bones (34–49%) with a local recurrence rate of 40–44% after primary treatment. Rarer sites of metastasis has been described in testis [27], mesentery [28] and tibia [29]. Secondary disease is an indicative feature for poor prognosis.

American Joint Committee on Cancer (AJCC) and the International Union for Cancer Control (UICC) in the year 2010 recommended MCC TNM Staging System. This was based on retrospective study included 5823 from the National Cancer Database registry [30], see Table I.

Histology

The microscopic features may show Merkel cells with scanty cytoplasm, a small dark polygonal nucleus with granular chromatin and a high mitotic rate [29]. Generally speaking, the histological features of MCC are similar to those of various other tumours, such as metastatic small cell lung carcinoma, blastic haematological malignancies of skin/soft tissue, and melanoma. Usually presented as composed of strands or nests of uniform, small round cells with scanty cytoplasm, round to oval nucleus with powdery dispersed chromatin, and inconspicuous nucleoli [32], see Figures 1 and 2.

Immunohistochemistry

A distinctive histochemical feature of MCC, is the expression of both neuroendocrine and epithelial markers. It is positive for CK-20, which is a sensitive marker for MCC and present in 90–100% of cases. As CK-20 is positive in some cases of extra-pulmonary small cell lung carcinoma (SCLC) it is essential that, the immunological study should include TTF-1 (Thyroid Transcription Factor-1), which expressed in 80–100% of SCLC but negative in MCC [33, 34]. CD56 is a sensitive marker for MCC but not specific [35]. Other immunohistochemical studies are need to confirm the diagnosis as the markers may coincide. One of those markers is CK-7(Cytokeratin-7) may be positive in carcinoid and basal cell carcinoma but negative in MCC. S-100 protein is another marker used to differentiate between malignant melanoma (usually positive) and MCC (usually negative) [36]. Synaptophysin is a trans-membrane channel protein of small pre-synaptic vesicles. MCC consistently shows positive immunoreactions to synaptophysin [37]. A combined features of cutaneous squamous cell carcinoma (SCC) and MCC noticed in some cases. As the MCC component often

Table I. Summary of the 2010 American Joint Committee on Cancer Merkel Cell Carcinoma staging system by SB Edge 2010

Clinical, before treatment		**Pathologic, after surgery**
	PRIMARY TUMOUR (T)	
TX	Primary tumor cannot be assessed	TX
T0	No evidence of primary tumor	T0
Tis	In situ primary tumor	Tis
T1	Less than or equal to 2 cm maximum tumor dimension	T1
T2	Greater than 2 cm but not more than 5 cm maximum tumor dimension	T2
T3	Over 5 cm maximum tumor dimension	T3
T4	Primary tumor invades bone, muscle, fascia, or cartilage	T4
	REGIONAL LYMPH NODES (N)	
NX	Regional lymph nodes cannot be assessed	NX
N0	No regional lymph node metastasis	N0
	Nodes negative by clinical exam*(no pathologic exam performed)	cN0
	Nodes negative by pathologic exam	pN0
N1	Metastasis in regional lymph node(s)	N1
	Micrometastasis**	N1a
	Macrometastasis***	N1b
N2	In transit metastasis	N2
	*Clinical detection of nodal disease may be via inspection, palpation and/or imaging	
	**Micrometastasis are diagnosed after sentinel or elective lymphadenectomy	
	***Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or needle biopsy	
	****In transit metastasis: a tumor distinct from the primary lesion and located either 1) between the primary lesion and the draining regional lymph nodes or 2) distal to the primary lesion	
	DISTANT METASTASIS (M)	
M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)	
M1	Metastasis beyond regional lymph nodes	M1
M1a	Metastasis to skin, subcutaneous tissues or distant lymph nodes	M1a
M1b	Metastasis to lung	M1B
M1c	Metastasis to all other visceral sites	M1C

ANATOMIC STAGE • PROGNOSTIC GROUPS

CLINICAL				**PATHOLOGIC**			
Group	**T**	**N**	**M**	**Group**	**T**	**N**	**M**
0	Tis	N0	M0	0	Tis	N0	M0
IB	T1	N0	M0	IA	T1	pN0	M0
IIB	T2/3	N0	M0	IIA	T2/3	pN0	M0
IIC	T4	N0	M0	IIC	T4	N0	M0
IIIB	Any T	cN1/N1b/N2	M0	IIIA	Any T	N1a	M0
IV	Any T	Any N	M1	IIIB	Any T	N1b/N2	M0
				IV	Any T	Any N	M1
Note: Isolated tumor nodes should be considered positive nodes				Note: Isolated tumor nodes should be considered positive nodes			

exists within the dermis, and not in the epidermis, dermis including biopsies should be carried out when evaluating potential NMSC (Non-Melanomatous Skin Cancer). This enables, not to miss an unrevealed deadly neuroendocrine element with a too superficial shave, causing delays in diagnosis and management of this aggressive and often fatal tumor [38]. Quantitative polymerase chain reaction (PCR) assay we used to detect MCPyV (Merkel Cell polyomavirus) DNA, this was found to be positive in 80% of cases [6, 16]. Most of the recurrence appears within the first six to 12

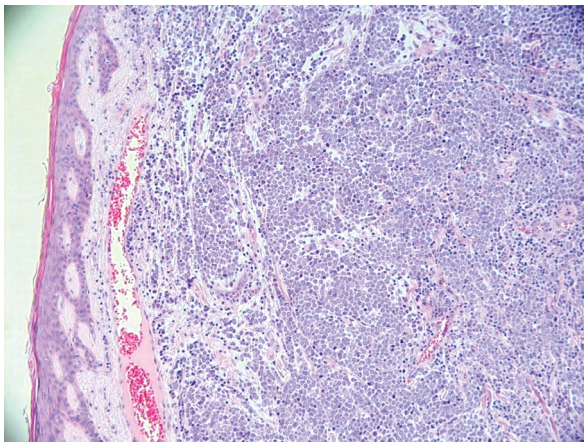

Figure 1. Merkel cell carcinoma — the tumour invades the dermis and subcutaneous tissue (10 × magnification)

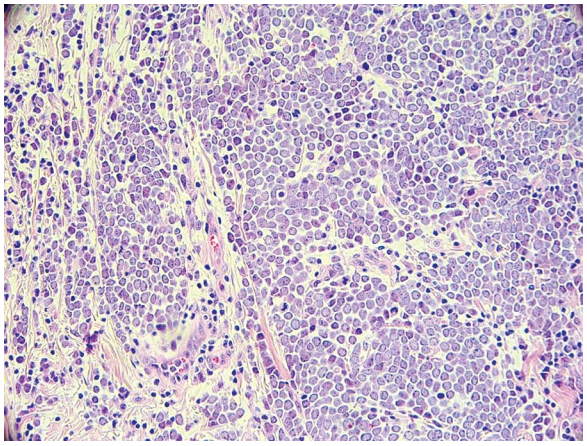

Figure 2. Poorly differentiated neoplasm, composed of medium-sized cells with dark nuclei and indistinct cytoplasm. There is apoptosis and brisk mitosis (20 × magnification)

months after the initial diagnosis [25]. Initial management of the patients has a significant impact on disease progression. This depends on the time of the first presentation and initiating the targeted treatment, this factor is decisive to disease prognosis. Immuno-histochemistry staining for cytokeratin 20 needed for diagnosis.

Treatment

Current optimal treatment is with radical surgical excision of the primary tumour, sentinel lymph node biopsy, ± regional lymph node dissection, radiotherapy, chemotherapy & immunotherapy [10, 39, 40].

Advanced Merkel-cell carcinoma often responds to chemotherapy, but responses are transient. Interfering with the programmed death 1 (PD-1) immune inhibitory pathway is of interest, because MCC often express PDL1, and MCPyV-specific T cells express PD-1. Using Pembrolizumab to block PD-1 revealed objective response rate of 56%. Responses were observed in patients with virus-positive tumours and those with virus-negative tumours [41]. MCC response to Nivolumab immunotherapy in the current clinical trials is promising [42].

Future

A trial of Pazopanib for Merkel cell skin cancer (UKM-CC-01). Phase 2 Recruitment started: 01/12/2012 and ended: 09/02/2016, currently awaiting results.

Conclusion

MCC is an aggressive cutaneous malignancy. The incidence of MCC is on the rise, and steadily ascend awareness along with moving forward in immuno-histochemistry staining techniques have greatly facilitated the diagnosis. The published reports heightened awareness of the association between MCC and other cancers. Further research is needed to explore this issue. Also there is a need to implement evidence-based management guidelines for MCC patients, especially that the inadequate initial management of many patients may contribute to the unfavourable disease progression and prognosis.

Conflict of interest: none declared

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