International Journal of Medical Research Professionals
P-ISSN: 2454-6356; E-ISSN: 2454-6364
DOI: 10.21276/ijmrp

IJMRP

Case Report .

Merkel Cell Carcinoma in a Patient with Previous History of Breast Cancer: A Case Report and Literature Review

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ABSTRACT

Merkel cell carcinoma (MCC) is a rare primary skin malignancy with very aggressive behaviour. This disease was first described by Cyril Toker in 1972. It is neuroendocrine in origin and has a high metastatic potential. There is ongoing research surrounding the highly specific diagnostic marker CK20, the pathogenesis of MCC related to Merkel Cell Polyomavirus (MCPyV) and the use of adjuvant therapy with chemotherapy and radiotherapy. In this paper, we discuss a case of a 77-year old female with MCC and a previous history of treated breast cancer.

Keywords: Merkel Cell Carcinoma, Toker Tumour, Breast Cancer, Malignant Melanoma, Merkel Cell Polyomavirus.

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Article History:

Received: 20-09-2017, **Revised:** 17-10-2017, **Accepted:** 15-12-2017

Access this article online	
Website: www.ijmrp.com	Quick Response code
DOI: 10.21276/ijmrp.2018.4.1.065	

INTRODUCTION

Merkel Cell Carcinoma is a rare primary neuroendocrine cancer of the skin, which usually arises in sun-exposed areas and mostly lies in the dermis layer.[1] It is characterised by very aggressive behaviour and high metastatic potential, and has a high recurrence rate (12-50%).[2] It was named after Dr Friedrich Sigmund Merkel (Figure 1), who first described the morphology of Merkel cells in the skin in 1875.There is a high prevalence of other malignancies associated with MCC, such as chronic lymphocytic leukaemia, non-Hodgkin lymphoma, breast, ovarian and small cell lung cancers (SCLC).[3,4]

This paper presents a case of MCC diagnosed in a patient with a previous history of treated breast carcinoma. To our knowledge, this is the second reported case in literature.

CASE PRESENTATION

A 77-year old lady presented with a painful right arm and a rapidly growing lump, showing significant growth in just a matter of weeks. Ten years earlier she had been diagnosed with cancer of the left breast, managed with a mastectomy, axillary clearance and implant reconstruction. Eight years after her breast cancer had been detected and treated, there was left axillary recurrence and an implant related infection. She subsequently underwent resection of the axillary recurrence, implant removal and postoperative chemotherapy. Clinically there was no local recurrence of breast cancer, however there was a suspicious isolated 3.5 cm lump in the right forearm. No enlarged local lymphadenopathy was present and a CT and bone scan showed no distant metastatic lesions. Surgical excision biopsy revealed a 30mm poorly differentiated malignant tumour, composed of medium-sized cells with dark nuclei and indistinct cytoplasm, together with apoptosis and brisk mitosis. The tumour invaded the dermis and subcutaneous tissue (Fig 2 and 3). The immune-histochemical profile showed a positive reaction to CK20 (Cytokeratin 20), Synaptophysin, Cam 5.2, and CD56. It was negative for CD45, S-100, HMB-45, CK7, TTF-1, GCDP-15 and oestrogen receptors. The overall features were of a Merkel Cell Carcinoma. Following surgery, the patient was referred for further oncology management. She received radiotherapy to the tumour bed site and is currently doing well.

DISCUSSION

Friedrich Sigmund Merkel (April 1845 - May 1919) was a leading German anatomist and histopathologist of the late 19th century (Figure 1). In 1875, he reported the first full description of Tastzellen (touch cells) which occur in the skin of all vertebrates. The origin is most likely skin mechano-receptor pluripotent stem

cells. Under the microscope, they appear as large clear-staining cells with lobulated nuclei at the dermo-epidermal junction, forming synapse-like contacts with enlarged terminal endings of myelinated nerve fibers and act as mechanoreceptors.[5] Three years later, Dr Robert Bonnet (1851–1921) who worked as an anatomist with Dr Merkel, suggested calling these cells Merkel cells.[6]

Fig 1: Friedrich Sigmund Merkel (1845-1919) [Reproduced with the kind permission of Associate Professor Boban Erovic, Department of Otolaryngology, Medical University of Vienna]

In 1972 Toker, who was born in South Africa and worked as a Professor of Pathology at the University of Maryland School of Medicine in Baltimore USA, reported the first case; this is why some papers call this disease Toker Tumour. He used the term "trabecular carcinoma" of the skin to describe a poorly differentiated carcinoma of the dermis and subcutaneous tissue.[4,7] He reported that the tumour cells showed large oval nuclei with vesicular chromatin and prominent nucleoli. The growth pattern is trabecular and there is column like-infiltration between dermal bundles. In 1980, Dr Wolff-Peeters proposed the name of Merkel cell carcinoma for the first time.[8]

Merkel cells are a subpopulation of cells derived from the neural crest, which thus excludes their development from the epidermis. There is sufficient evidence that Merkel cells with associated nerve terminals function as mechanoreceptor units.[5] MCC arises in the basal layer of sun-exposed skin areas and in the outer root sheath of hair follicles, as well as digits, lips and penis.[4,9] MCC is a disease of the fair-skinned elderly population, presenting more often in males than in females.[10] MCC is associated with risk factors, including sun-exposure, UV-B radiation[2,4,11], psoriasis treated with UV-A and methosxsalen, immunosuppression, radiotherapy and Merkel Cell Polyomavirus (MCPyV).[12,13] The USA incidence among the white population is 0.23 per 100,000 but seems to be lower among the black population (0.01 cases per 100,000), with only a few cases reported in this population group.[14] The UK data which has been reported in the National Cancer Intelligence Network Report for Rare Skin cancers (Nov 2011) shows incidence rates of 0.1-0.2 per 100.000 population.[15]

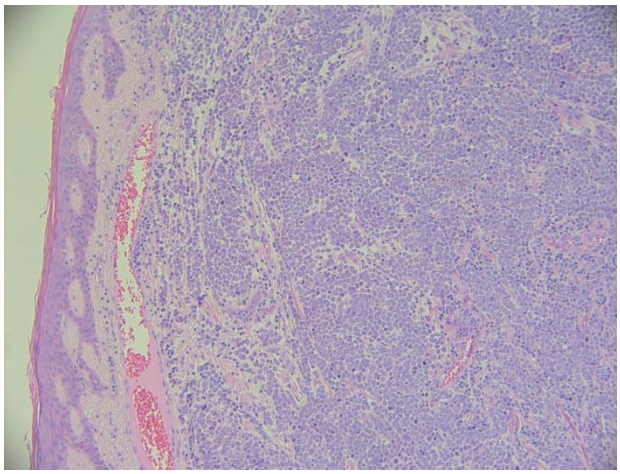

Fig 2: Merkel Cell Carcinoma. The tumour cells invade the surrounding tissues and are seen in the dermis and subcutaneous tissue (10x magnification).

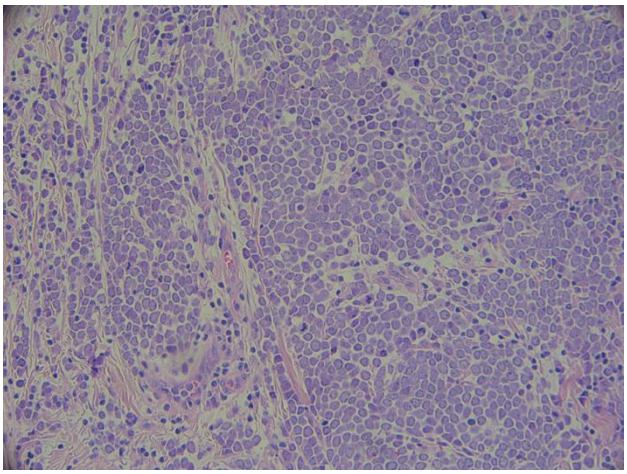

Fig 3: Poorly differentiated malignant cells, composed of medium-sized cells with dark nuclei and indistinct cytoplasm. There is apoptosis and brisk mitosis (20x Magnification).

Clinically it may present as a slowly or rapidly growing skin nodule in sun exposed areas, such as the head and neck (30-50%), legs (25%), arms (21%) and trunk (10%).[16,17] MCC has also been reported in non sun-exposed areas, such as the gluteal region[18], tongue[19], penis[20] and vulva.[21] It may be a painless, firm lump that can be red-purple in colour or may ulcerate, and may be associated with local lymphadenopathy.

Heath et al [2008] suggested an acronym AEIOU which denotes the five most common clinical features: AEIOU - asymptomatic/lack of tenderness, expanding rapidly (≤ 3 months), Immunosuppression, older than age 50, and location on a UV-exposed site.[17]

The common sites of the secondary disease are the skin (28%), lymph nodes (27%), liver (13%), lung (10%), bones (10%), and brain (6%).[14] Rarer sites of metastasis have been reported in testes[22], mesentery[23], rectum[24], tonsils[25], tibia[26] and ovaries.[27] The presence of secondary disease indicates unfavourable treatment outcome and poor prognosis.

Microscopically MCC is seen as blue round small cells with scanty cytoplasm, basophilic nuclei, frequent mitosis and a high index of apoptosis [Ring]. MCC has three histological subtypes. The first is the intermediate variety called small cell variant which resembles SCLC (Small Cell Lung Carcinoma). The second is the intermediate type characterised with vesicular, basophilic nuclei

with prominent nucleoli and high mitotic activity. The third subtype is trabecular MCC. It is rare and seen as a small component of a mixed variant [Jaeger]. The small cell variant should not be mistaken for small-cell lung carcinoma, carcinoid tumour, malignant lymphoma, primitive endocrine tumours, neuroblastoma, small cell osteosarcoma, Ewing's sarcoma or small-cell melanoma.[28]

In 2008, Feng et al, from University of Pittsburg USA founded a fusion transcript between previously undescribed virus T antigen and a human receptor tyrosine phosphatase in resected MCC specimens. Further analysis revealed a virus that they called Merkel cell Polyomavirus (MCPyV).[29] The reports substantiated that about 80% of MCC express evidence of MCPyV.[30] The presence of MCPyV DNA is tested by using quantitative real-time Polymerase Chain Reaction (PCR) and is positive in 80% of the cases.[10,31]

Immuno-histochemical studies are essential for MCC diagnosis; it shows positivity for cytokeratins 8, 18, 19 and 20. The cytokeratin 20 (CK-20), which is a low molecular weight cytokeratin (CAM 5.2), is associated with high positivity rate for MCC irrespective of the subtype. CK-20 may be positive in extra-pulmonary small cell lung carcinoma (SCLC). It will be necessary to stain the sample for TTF-1 (Thyroid Transcription factor-1), which is almost always positive in SCLC, however negative in MCC.[32,33] CK-7 will be very helpful; it is positive in carcinoid and basal cell carcinoma, but negative in MCC. S-100 protein, is a marker which is usually positive in malignant melanoma and SCLC, but negative in MCC.[34] The leukocyte common antigen {LCA) is negative in MCC but positive in lymphoma.[35] Another highly sensitive marker for MCC is neuro-filament protein (NFP) immune-stains which are also frequently used in MCC diagnosis.[36] There are other markers which show some positivity in MCC, such as chromogranin, synaptophysin (Trans-membrane Channel Protein)[37] and neuron-specific-enolase (NSE).[8]

There is a higher prevalence of other malignancies associated with MCC, such as chronic lymphocytic leukaemia, non-Hodgkin lymphoma, breast, ovarian and small cell lung cancers (SCLC).[3,4] We thought our paper presented the first case of Merkel cell carcinoma associated with breast cancer, however we found that *Vladimiora et al* reported a case in 2016. The MCC of breast skin is less frequent than other sites; it may be a primary or metastatic lesion of MCC started elsewhere.[38]

MCC is a highly aggressive skin cancer with a mortality of approximately 33% at 3 years, higher than that of melanoma (approximately 15%) [Heath 2008]. Surgery is the primary management option in early disease, either by wide local excision with 1 -3 cm margin and intra-operative sentinel lymph node biopsy, or using Moh micrographic surgery with pre-operative sentinel lymph node biopsy.[8,28,39,40] As MCC is radiosensitive[41], adjuvant treatment with radiotherapy is indicated after surgery, where the primary radiotherapy is indicated for palliation.[42] The local recurrence is similar for patients treated with surgery only (14%) compared with surgery and adjuvant radiotherapy (12%).[22,43] Systemic chemotherapy is considered part of the multimodal therapy concept in metastatic disease in addition to surgery and radiotherapy.[44]

The concept of viral oncogenesis related to Merkel Cell Polyomavirus, opens the door to immunotherapy and antiviral treatment. This involves the use of Pembrolizumab and Nivolumab as immunomodulators.[45,46] The use of interferon-α (IFN- α), anti-CD56 antibodies and TFN- α as antiviral agents has also been reported.[47]

Future Treatments

Use of immunogen anti-CD56 monoclonal antibody shows promising therapeutic results in current clinical trials.[8]

UKMCC-01 is a trial looking at the use of Pazopanib in management of metastatic MCC. Recruitment started 01/12/2012 and ended 09/02/2016; the results report is currently awaited.[48]

CONCLUSION

Merkel Cell Carcinoma is a rare aggressive neuroendocrine skin malignancy. The relationship between MCC and Polyomavirus is seen in almost 80% of the cases. Surgery remains the mainstay of management. The published reports heighten awareness of the association between MCC and other cancers. This paper presented the occurrence of Merkel Cell carcinoma in a patient with a history of breast cancer; this is the second report of such a condition, as the first was reported by *Vladimiora et al* in 2016. As breast cancer is more common than MCC, is the coexistence of both conditions a coincidence or is there an association? More work and research is needed to explore this issue.

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Source of Support: Nil. **Conflict of Interest:** None Declared.

Cite this article as: Abdalla Saad Abdalla Al-Zawi, Andrzej Ratajczak, Soad Eldruki, Kinga Zastawna, Elizabeth Tan. Merkel Cell Carcinoma in a Patient with Previous History of Breast Cancer: A Case Report and Literature Review. Int J Med Res Prof. 2018 Jan; 4(1):313-16.DOI:10.21276/ijmrp.2018.4.1.065