

Merkel cell carcinoma - A retrospective case series

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ABSTRACT Merkel cell carcinoma (MCC) is a rare cutaneous malignancy. Excessive exposure to sunlight and ultraviolet (UV) radiation, immune suppression and advanced age are the major risk factors for MCC. It typically presents in the head and neck region (50%), followed by extremities (40%) and rarely at other sites (<10%). In 2008, Merkel cell polyomavirus (MCV) was linked to the development of Merkel cell carcinoma (MCC). MCC is included in the differential diagnosis of small blue cell neoplasms, composed of monomorphous population of cells with round-to-oval nucleus and scant cytoplasm. The tumor cells co-express epithelial and neuroendocrine markers. ALK (Anaplastic lymphoma kinase) expression is frequently seen in MCC and correlates with the etiopathology of Merkel cell polyomavirus (MCV). On a retrospective search through our database, we found ten cases of MCC over a period of three years from 2016 to 2019. Three of the ten cases were at sites of chronic sun exposure. Eight of the ten patients were male. Two of the ten patients had recurrences; one within a year. Five of the ten patients had metastatic disease. All ten cases showed immunoexpression of CK20, Synaptophysin and Chromogranin. ALK-1 expression could be ascertained in six of the cases and was positive in all of them. This case series highlights a relatively uncommon Polyoma virus associated carcinoma. The significance of ALK immunopositivity in MCC, its implied correlation with Merkel cell polyomavirus (MCV) etiopathogenesis and the possibility to use it as a novel therapeutic target needs further exploration.

KEYWORDS Merkel cell carcinoma (MCC), Merkel cell polyoma virus (MCV), ALK (Anaplastic lymphoma kinase)

Introduction

Merkel, a professor of anatomy at the University of Rostock, Germany, described “Tastzellen” (touch cells)—later known as Merkel cells—in the epidermis of domestic animals and humans, for the first time in 1875[1]. In 1972, Toker first reported a case series study of five patients with “trabecular carcinoma” and recognized a “distinct pathological entity”[2]. It took Tang and Toker another six years to determine that trabecular carcinoma “most probably” derives from Merkel cells[3].

The Merkel cell is a specialized neuroepithelial cell that may have a touch receptor function and is present within the basal

cell layer of the epidermis, oral mucosa, outer follicular sheath of hair follicles and sweat ducts[4].

Merkel cell carcinoma is a highly aggressive neuroendocrine skin tumour that typically presents as a rapidly growing, painless, flesh-coloured or bluish-red intracutaneous nodule. The most common clinical features of MCC are summarized by the acronym “AEIOU”: Asymptomatic, Expanding rapidly, Immune suppression, Older than age 50 and UV-exposed site on a fair-skinned individual. The most frequent sites of involvement are in the head and neck region (50%), followed by extremities (40%) and rarely at other sites (<10%)[5-8].

In 2008, Merkel cell polyomavirus (MCV) was linked to the development of MCC[9]. Clonal integration of MCV DNA into the host genome is a causal factor for the development of the majority of MCC tumors[10]. MCV is an abundant virus frequently detected on healthy human skin, suggesting that its infection is widespread in the general population[12-14].

MCC is included in the differential diagnosis of small blue cell neoplasms, composed of a monomorphous population of cells with a round-to-oval nucleus and scant cytoplasm. The nucleus contains primitive, diffusely dispersed chromatin and

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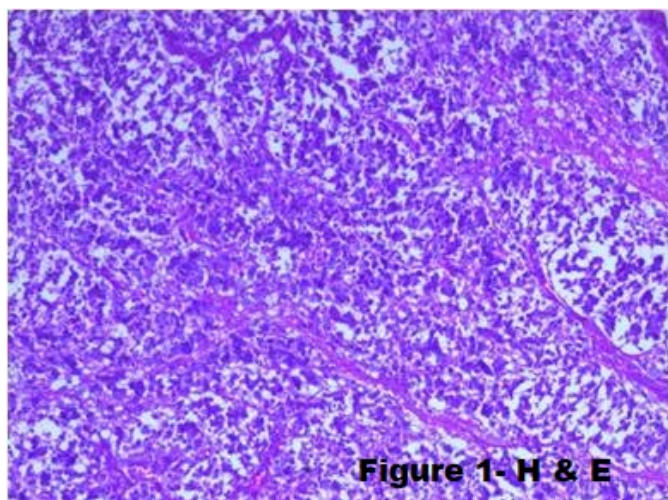


Figure 1:

mitoses are usually numerous. Three morphological patterns are noted in MCC, i.e. solid, trabecular and diffuse (Figure 1); amongst which the diffuse pattern is most commonly seen[17].

The tumour cells co-express epithelial and neuroendocrine markers. Wide spectrum cytokeratins (AE1/3, CAM5.2) and cytokeratin 20 (CK20) are present typically either as paranuclear dot-like or diffuse cytoplasmic staining. The neuroendocrine markers of MCC include synaptophysin, chromogranin A and others. The closest differential diagnosis is small cell lung carcinoma (SCLC)- which shows TTF-1 expression and is immunonegative for CK20.

ALK immunoreexpression is frequently seen in MCC and correlates with the etiopathology Merkel cell polyomavirus (MCV)[18]. ALK expression is absent or very low in normal skin. There are three different anaplastic lymphoma kinase antibody clones (D5F3, 5A4, and anaplastic lymphoma kinase 1)[20-23]. Previous IHC studies suggest that D5F3 is the most sensitive clone in detecting ALK expression in MCC tumors[24]. Studies have further identified ALK as the most frequently over-expressed gene among 50 cancer-related genes in MCC cases[23]. Interestingly, the authors found no evidence of fusion events, raising the possibility that ALK overexpression in Merkel cell carcinoma arises from genetic or epigenetic events[24].

Materials and Methods

On a retrospective search through our database, we found ten cases of MCC over three years from January 2016 to January 2019. We searched our electronic patient database using the following keywords: "Merkel cell carcinoma" and "Merkel cell". Inclusion criteria were confirmed histopathologic diagnosis of Merkel cell carcinoma. Both biopsy and excision specimens were included. For each patient, the following parameters were assessed: site of involvement, age, sex, recurrence, metastasis, ALK expression on immunohistochemistry (IHC), treatment modality and overall survival. ALK-1 clone was used for IHC.

Case reports

The retrospective search yielded ten cases, the details of which are enumerated herewith. The case table attached summarizes the ten cases with their demographics and disease status.

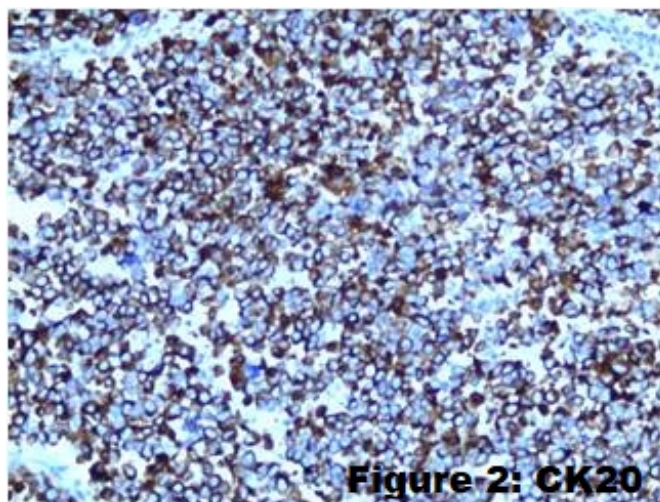


Figure 2: CK20

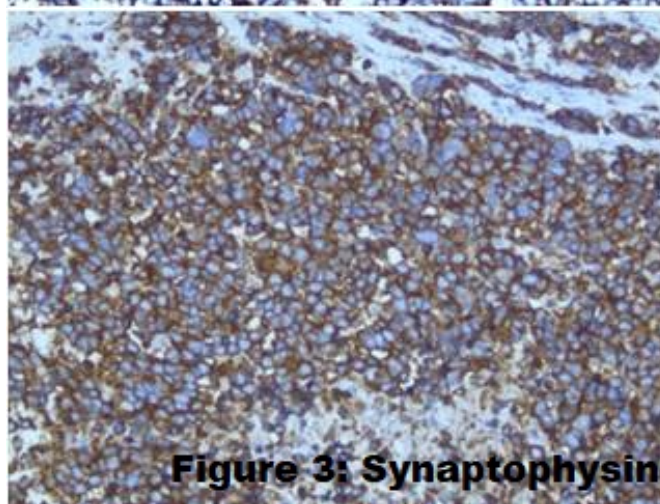


Figure 3: Synaptophysin

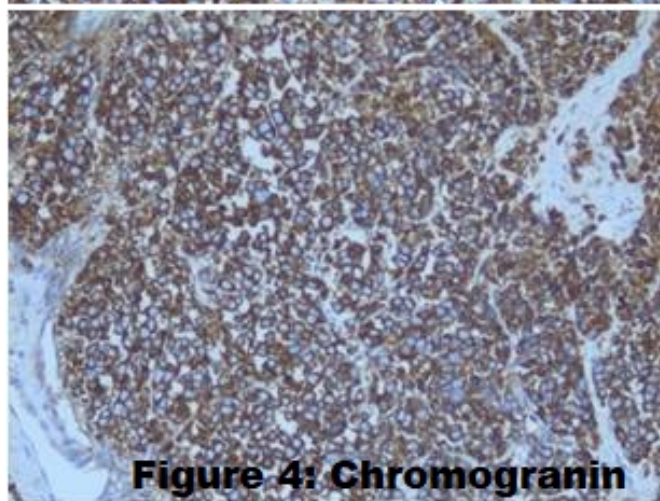


Figure 4: Chromogranin

Figure 2,3,4:

Table 1

Case no.	Age(in years)/ Sex	Site of involvement	Treatment modality	Recurrence	Metastasis	ALK expression	Overall survival
1.	86/M	Left thigh	Wide local excision	No	No	N/A	Remission since 2years
2.	51/M	Right hip	Wide local excision followed by chemotherapy and radiotherapy	No	No	N/A	Remission since 2years
3.	87/F	Left upper eyelid	Wide local excision	Yes (within <2years)	Yes (to lymph nodes)	N/A	Death (due to co-morbidity)
4.	71/M	Scalp	Wide local excision followed by chemotherapy	Yes- twice (within <1year)	Yes (to lymph nodes)	N/A	Recurrent disease on the scalp-on treatment
5.	65/M	Right abdominal wall nodule	Wide local excision followed by chemotherapy and radiotherapy	No	No	Positive	Remission since 1 year
6.	82/M	Left inguinal lymph node- primary site unknown	Excision biopsy	Patient lost to follow up	Yes (metastatic lymph node)	Positive	Patient lost to follow-up
7.	55/F	Right upper eyelid	Wide local excision followed by chemotherapy and radiotherapy	No	No	Positive	Ongoing treatment
8.	65/M	Right parotid region	Wide local excision	No	Yes (to lymph nodes)	Positive	Remission
9.	63/M	Deep axillary mass	Wide local excision	No	Yes(to lymph nodes)	Positive	Ongoing treatment
10.	51/M	Axillary Lymph node	Excision biopsy	No	Yes(to lymph node)	Positive	Ongoing treatment

Results

Three of the ten cases were at sites of chronic sun exposure, three were on the extremities, and two were at uncommon sites. Eight of the ten patients were male. Five of the ten patients had metastatic disease. Two of the ten patients had recurrences; one within a year. One patient expired within a year of the recurrence. All ten cases showed immunoexpression of CK20, Synaptophysin and Chromogranin (Figure 2, 3 and 4). ALK-1 expression could only be ascertained in six of the cases and was positive in all six cases (Figure 5). In three of the cases, primary skin involvement could not be demonstrated.

Discussion

The case series demonstrates concordance with the published literature about MCC being predominantly found in elderly males¹⁹. The mean age of patients in our cohort was 77 years which corroborates with the published literature^[19].

While most cases present in sun-exposed areas, it is also

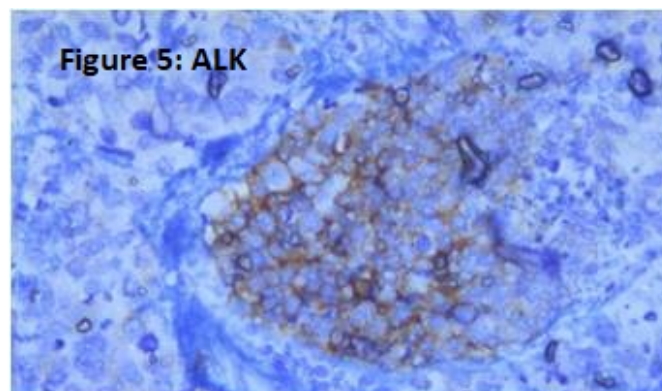


Figure 5:

important to note that this neoplasm may present in areas of minimal sun exposure. In our series, only three lesions were found on sun-exposed areas, while the others were on relatively less sun-exposed areas.

A retrospective study of 85 cases of MCC by Eng TY et al. showed that surgery remains the primary modality for the treatment and adjuvant radiation therapy +/- systemic chemotherapy reduces local recurrence[20]. Standard of surgical care for MCC has traditionally been wide local excision (WLE) and at early stages, surgery alone may be sufficient[21-23].

We report here a single centre retrospective analysis. The demographics of our patient cohort differ from other retrospective reports; there were no immunosuppressed patients, which, however, could be explained by the relatively small patient cohort.

Our results lack statistical significance due to the low number of patients and events. Nevertheless, we believe that increased awareness of MCC is essential to ensure optimal initial management. Failure to do so can lead to a higher number of surgical interventions.

Conclusion

This case series highlights a relatively uncommon Polyoma virus-associated carcinoma. The significance of ALK immunopositivity in MCC, its implied correlation with Merkel cell polyomavirus (MCPyV) etiopathogenesis and the possibility to use it as a novel therapeutic target needs further exploration.

Compliance with ethical standards

The authors confirm that the work presented complies with ethical standards.

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Conflict of interest

The authors declare that they have no conflict of interest.

Contributions

1. Dr. Kanica Chaudhary: Formulation of the manuscript, corresponding author.
2. Dr. Jay Mehta: Conceptualisation of the study, editing of the manuscript, reporting pathologist of some of the cases included in the study.
3. Dr. Shilpa Prabhudesai: Editing of the manuscript, reporting pathologist of some of the cases included in the study.
4. Dr. Vinita Pant: Reporting pathologist of some of the cases included in the study.
5. Dr. Puja Khanna: Digital images, assisted in the ground-work for the study.
6. Dr. Anita Borges: Head of the institute, reporting pathologist of some of the cases included in the study.

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