Short communication

Prognostic significance of tumour budding in Merkel cell carcinoma

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Prognostic factors in Merkel cell carcinoma (MCC) are scarce. Tumour budding (TB) has been shown to have a prognostic role in different cancers but has not been explored in MCC. We aimed to determine if TB influences survival in MCC.
We performed a retrospective evaluation of 45 cases of MCC in a cancer centre. This included a survival analysis involving TB in patients with MCC, and we searched for variables associated with TB.
The mean age of the patients was 69 years. Histologically, the average Breslow was 11.36 mm, and the mean mitotic rate was 31.9 mitoses/mm2. The diagnosis was made in clinical stages I and II in 40% of cases, 22.2% in stage III, and 37.8% in stage IV. Tumour budding was low (< 5 buds/0.785 mm^2) in 44.4% of cases and high (> 10 buds/0.785 mm^2) in 24.4%. There were no clinical or pathological features associated with high TB. Among the prognostic factors for 5-year survival, we found that tumour size and clinical stage were statistically associated with survival ($p = 0.031$ and 0.021), but TB was not.
No clinical or pathological characteristics of MCC are associated with any degree of TB. Tumour budding does not influence overall survival.

Key words: Merkel cell carcinoma, skin cancer, tumour budding, prognosis.

Introduction

Merkel cell carcinoma (MCC) is a rare and aggressive endocrine-differentiated skin cancer that commonly presents as a painless erythematous nodule with or without ulceration. Dermoscopic features include linear, irregular, and polymorphous vessels, poorly focused vessels, and milky-pink areas [1]. It is often confused with basal cell carcinoma. It is more common in elderly Caucasians in sun-exposed areas such as the head and neck [2].

The exact pathogenesis of MCC is poorly understood. Increased ultraviolet radiation is associated with MCC incidence rates [3], and immunosuppression has also been associated with it. In 2008, Merkel cell polyomavirus was found to be associated with this tumour. However, its prevalence varies depending on the region (8% in North America and 80% in Asia) [4].

Prognostic factors in MCC are scarce. Tumour budding (TB) has shown a prophetic role in different cancers but has not been explored in MCC. A unique and fundamental characteristic of malignant neoplastic cells is the ability to invade and metastasize; the first step in this process is the dissociation of some of these cells from the invading front of the tumour; various researchers have highlighted the histopathological representation of this phenomenon using multiple terms; the most accepted and, until relatively recently, agreed, is the term TB. Tumour budding has taken on great relevance in recent years, given its relationship with vascular invasion, metastasis, and prognosis in terms of recurrence and

survival. In addition, it has been closely associated with the phenomenon called epithelial-mesenchymal transition.

The definition of TB has been a controversial issue throughout its development, even today, when there is a consensus on the matter [5]. The most widely used definition refers to an isolated tumour cell or groups of up to 4 cells separated from the glands of the invading front of the tumour [6].

Our objective is to determine if TB is a factor that impacts the survival of patients with MCC.

Material and methods

Population

Patients with pathologically confirmed MCC were identified in 2005–2018, and their medical records were reviewed. We recorded the following characteristics: age, sex, primary location, staging, treatment, and oncological outcomes. Patients with MCC were staged according to the 8th American Joint Committee on Cancer system [7]. Tumour budding was evaluated in the same way that was described in colorectal cancer [6] by 2 pathologists with consensus in the case of discordant cases.

The research committee of our institution approved this study (ICAN/18/20).

Treatments

Patients with locoregional MCC underwent wide local excision of the primary tumour with or without lymph node management. Adjuvant chemotherapy or radiation therapy was selected and performed at the physicians' discretion based on the pathology reports. Palliative chemotherapy (cisplatin and etoposide) and immunotherapy were chosen for patients with inoperable MCC.

Statistical analysis

Continuous variables are presented as median with minimum and maximum, while categorical data are presented as count and percentage. Overall survival was defined as the time from diagnosis to death from any cause or to the last follow-up. Survival curves were plotted using the Kaplan-Meier method, and survival analysis was performed by comparing survival curves with the log-rank test. Statistical analyses were performed using SPSS version 22.0 software.

Results

We identified 45 cases of MCC. The average follow-up was 31.11 months; to date, 68.9% of patients are alive. The minimum age was 40 years, and the maximum age was 91 years; the mean was 69 years, with a higher frequency of presentation in women (25 versus 20 men). The most frequently affected anatomical regions were those not photoexposed (55.6%); histologically, an infiltrative invasive front was found, primarily present in 68.9% of cases, with an average Breslow of 11.36 mm, and the average mitotic rate was 31.93 mitoses/mm^2. The diagnosis was made in early clinical stages (EC I and II) in 40% of cases, 22.2% in locally advanced stage (ECIII), and 37.8% in metastatic clinical stage, most of whom received adjuvant treatment (55.6%), which consisted of chemotherapy and radiotherapy.

Tumour budding in most cases was low ($<$ 5 buds/0.785 mm^2, 44.4% of cases) compared to 24.4% of those with a high budding rate ($>$ 10 buds/0.785 mm^2). As shown in Table I, no clinical or pathological features were associated with high TB.

Among the prognostic factors for 5-year survival, we found that tumour size and therefore clinical stage were statistically significant ($p = 0.031$ and 0.021, respectively), whereas TB was not associated with survival (Table II).

Discussion

In our study of 45 cases of MCC, we did not identify clinical or pathological characteristics associated with the various degrees of TB. Likewise, TB did not influence survival.

Tumour budding on the invasive front has recently been suggested as a potential index of aggressiveness and poor prognosis for various types of cancer [1–5]. An essential advantage of this index is its simplicity and reproducible measurement. It is easily adapted to routine histopathological examination based on haematoxylin and eosin staining without the need for additional expensive techniques. This feature is essential and may have therapeutic implications for patients with MCC. In this study, consistent with previous reports in other cancers, good reproducibility was achieved for the assessment of TB based on intra- and interobserver agreement studies ($k = 0.880$ and 0.717).

To date, the prognostic implication of TB in MCC has not been investigated. In our study, there is no evidence that tumour budding has a prognostic significance in overall survival. We are aware that there are several limitations to our report. First, there are potential biases due to the retrospective nature of our study. Second, the findings could even be biased because, in a concentration and national reference hospital, the percentage of tumours with a poor prognosis could be higher due to referral than in daily outpatient practice.

Table I. Clinicopathological features of 45 patients with Merkel cell carcinoma according to tumour budding groups

Parameters	Tumour budding group			*p*-value*
	Low (0–4 buds/0.785 mm²)	Intermediate (5–9 buds/0.785 mm²)	High (≥ 10 buds/0.785 mm²)	
Age (years), median (min–max)	74 (49–91)	70 (42–86)	62 (40–91)	0.608
Breslow [mm], median (min–max)	13 (4–27)	9 (2–24)	9 (2–20)	0.574
Mitosis, *n*, median (min–max)	36 (1–230)	14 (0–49)	13 (2–55)	0.154
Sex, *n* (%)				0.328
Male	11 (55)	6 (42.9)	3 (27.3)	
Female	9 (45)	8 (57.1)	8 (72.7)	
Sun exposure, *n* (%)				0.641
No	9 (45)	5 (35.7)	6 (54.5)	
Yes	11 (55)	9 (64.3)	5 (45.5)	
Clinical stage, *n* (%)				0.270
I	2 (10)	5 (35.7)	3 (27.3)	
II	3 (15)	4 (28.6)	1 (9.1)	
III	7 (35)	1 (7.1)	2 (18.2)	
IV	8 (40)	4 (28.6)	5 (45.5)	
Tumour size, *n* (%)				0.611
< 2 cm	7 (35)	8 (57.1)	4 (36.4)	
2–5 cm	4 (20)	2 (14.3)	1 (9.1)	
> 5 cm	9 (45)	4 (28.6)	6 (54.5)	
Invasive front, *n* (%)				0.155
Infiltrative	11 (55)	12 (85.7)	8 (72.7)	
Pushing	9 (45)	2 (14.3)	3 (27.3)	
Breslow groups, *n* (%)				0.350
< 5 mm	2 (10)	5 (35.7)	2 (18.2)	
5–10 mm	7 (35)	3 (21.4)	5 (45.5)	
> 10 mm	11 (55)	6 (42.9)	4 (36.4)	
Mitosis groups, *n* (%)				0.127
< 25 /mm²	6 (30)	8 (57.1)	7 (63.6)	
> 25 / mm²	14 (70)	6 (42.9)	4 (36.4)	
Adjuvant, *n* (%)				0.076
No	12 (60)	10 (71.4)	3 (27.3)	
Yes	8 (40)	4 (28.6)	8 (72.7)	
Progression, *n* (%)				0.640
No	10 (50)	9 (64.3)	7 (63.6)	
Yes	10 (50)	5 (35.7)	4 (36.4)	
Outcome, *n* (%)				0.155
Alive	11 (55)	12 (85.7)	8 (72.7)	
Dead	9 (45)	2 (14.3)	3 (27.3)	

Table II. Factors associated with survival in 45 patients with Merkel cell carcinoma

Parameters	5-year survival (%)	*p*-value
Sex		0.444
Male	62.9	
Female	52.1	
Sun-exposure, *n* (%)		0.195
No	43.8	
Yes	75.2	
Clinical stage, *n* (%)		0.021
I	85.7	
II	100	
III	37.5	
IV	36	
Tumour size, *n* (%)		0.031
< 2 cm	74.2	
2–5 cm	83.3	
> 5 cm	21	
Invasive front, *n* (%)		0.807
Infiltrative	60	
Pushing	55	
Breslow groups, *n* (%)		0.649
< 5 mm	74	
5–10 mm	66.2	
> 10 mm	42.6	
Mitosis groups, *n* (%)		0.573
<25 /mm^2	63.6	
> 25 / mm^2	54.9	
Adjuvant, *n* (%)		0.930
No	61	
Yes	55.2	
Progression, *n* (%)		0.025
No	79.2	
Yes	33.9	
Tumour budding groups, *n* (%)		0.511
0.4	48.4	
5–9	77.4	
10 or more	63	
High tumour budding (>10 buds/0.785 mm^2)		0.961
No	56.4	
Yes	63	

Conclusions

No clinical or pathological characteristics of MCC are associated with any degree of TB. Tumour budding is not related to overall survival in MCC.

The authors declare no conflict of interest.

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