MERKEL CELL CARCINOMA: A SINGLE-INSTITUTION RETROSPECTIVE CASE SERIES ANALYZING CD271 EXPRESSION WITH A FOCUS ON ITS PROGNOSTIC ROLE

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Dear Editor,

merkel cell carcinoma (MCC) is an aggressive primary cutaneous neuroendocrine neoplasm of increasing incidence, which occurs most frequently in elderly patients.

The carcinogenesis process involves viral integration of the retinoblastoma protein sequestering Merkel cell polyomavirus, and ultraviolet radiation-induced mutations [1]. Prognostic factors for recurrence and survival are rarely reported and, in most cases, they are nonconclusive. They include age, location, size, immunosuppression, stage of disease, mitotic index, cell size, angiolymphatic invasion, and immunoreactivity for CD44, ki67, p53, and p63 [2, 3].

CD271 (also known as NGFR, p75NTR, TNFRSF16, and Gp80-LNGFR), a protein with tumour-initiating properties and progression potential [4], has not been specifically studied in MCC.

We examined the CD271 immunohistochemical expression in our MCC cases to investigate the possible involvement of this marker in the oncogenesis and prognosis of MCC.

We assessed 8 tumour samples obtained from 8 patients (5 women and 3 men), with a mean age of 83 years (range, 79-89 years) referred to our institution between 2006 and 2017. MCC presented most frequently as a single erythematous nodule with a necrotic or ulcerated surface, from 1 to 4 cm of diameter (Fig.1).

Three out of 8 patients had a relapse (mean time before recurrence, 2.4 months) (range, 2 weeks-4 months); one had regional lymph node recurrences; two developed systemic metastases and died of MCC (Table 1).

Histologically, the trabecular pattern was the most common observed, with tumours predominantly localized in the dermis and in one case invading deeply the subcutis.

Cytomorphology showed small/medium cells with scant cytoplasm, and round nuclei with

dispersed chromatin (Fig.2a, d). Many mitoses (>5 per high-power field) and necrotic areas were noted respectively in 8 and 6 cases.

Immunohistochemical evidence of neuroendocrine differentiation and immunopositivity for cytokeratin 20 were present in all cases (Fig.2b, e).

CD271 expression was assessed by comparing blind results obtained from three distinct observers, who evaluated both percentage of CD271 positive neoplastic cells and staining intensity (+=weak, ++= medium, +++=strong).

In our series, CD271 was weakly expressed in all lesions, with a higher percentage in patients who had metastases, shorter survival rates, and death from disease (Table 1, Fig.2 c, f).

In the literature, amongst immunohistochemical markers, CD44, p53, Ki67, and p63 have been associated with a poor prognosis [1, 3] but there are no reported studies about the expression of CD271 in MCC.

Based on our results, a CD271 expression seem to correlate with shorter disease-free survival and disease-specific survival.

According to previous observations, this marker influences stem cell functions, like tumorigenicity and plasticity [4].

In fact, CD271 positive melanoma stem cells have shown correlation with a higher metastatic potential and worse prognosis in immunodeficient mice, and with metastases but not prognosis in humans [5].

Recent findings provide new insight in the role of CD271 in DNA repair, drug response and melanoma metastatic processes in a CD271-associated signalling network potentially regulated by p53 [4].

Even though they are preliminary results that should be validated by a larger sample, CD271 could be a useful marker in prognostic assessment of patients with MCC for the more aggressive nature of MCC with increased expression of CD271 compared to cases with a lower score.

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Table 1 Patients' characteristics at presentation, clinical course, and CD271 expression.

Patient N./Year of presentation	Age(y)/sex	Site	Clinical presentation/Size (mm)	TNM Stage at diagnosis	Recurrence/ Primary therapy	Alive or dead/ mo	Past skin cancers/ other malignancies	CD271 expression
1/2006	79/F	Head	Firm, red nodule/ 10	IA	No/ Wide excision	Alive/138	None	50
2/2012	81/M	Head	Firm, necrotic-ulcerative nodule/ 35	IV	Yes (locoregional and distant)/ Wide excision+chemo+RT	Dead/8 due to MCC	None	70
3/2013	87/F	Left leg	Multiple red nodules/ from 10 to 20	IV	Yes (locoregional and distant)/None	Dead/4 due to MCC	Breast cancer 40 year before	70

4/2015	83/M	Left leg	Two subcutaneous nodules/ from 10 to 15	IA	No/ Wide excision	Alive/24	None	50
5/2016	80/F	Buttock	Firm, necrotic-ulcerative nodule/ 40	II	Yes (locoregional)/wide excision+RLND	Alive/14	Kaposi sarcoma	70
6/2016	79/F	Thigh	Firm, red nodule/ 25	IB	No/ Wide excision	Alive/12	None	50
7/2017	89/M	Abdomen	Firm, red nodule/ 15	IA	No/Wide excision	Dead/5 due to MM metastases	SCC, MM	50
8/2013	87/F	Right leg	Firm, red nodule/ 15	IA	No/Wide excision	Dead/9 of heart disease	None	50

6) RT: radiotherapy; RLND: regional lymph node dissection; SCC: squamous cell carcinoma; MM: malignant melanoma

Figure 1 Clinical pictures of Merkel cell carcinoma in our case series: (a, b, c) rapidly growing erythemato-violaceous nodules with an ulcerated surface and areas of necrosis, (d) an unusual presentation with a subcutaneous skin-coloured nodule.

Figure 2 Morphological and histochemical characteristics of Merkel cell carcinoma. Haematoxylin and eosin morphological features (a, d): (a) Dermal infiltrating tumour with round monomorphic cells arranged in small nests with a non-cohesive growth pattern (Original magnification ×200); (d) Neoplastic cells show vesicular nuclei with small nucleoli and dispersed chromatin (Original magnification ×400).

(b, e) Distinct perinuclear cytoplasmatic dotlike positivity with cytokeratin 20. (b Original magnification ×200, e Original magnification ×400).

(c, f) Neoplastic cells were found to be positive for CD271 (NGFR5, Ab1, Neomarkers; dilution 1:200) with variable percentage in all cases. (c Original magnification ×200, f Original magnification ×400).