Merkel cell carcinoma. Study of five cases

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Abstract

Merkel cell carcinoma (MCC) is a rare malignant tumor, locally aggressive, that tends to metastasize to lymph nodes and distant sites. These cells resemble neuroendocrine cells in ultrastruture and immunohistochemistry. The etiopathology is unknown, but an association with other epithelial tumors has been reported, and recently, virus replication within the tumor was demonstrated. Risk factors are clinically characterized by the acronym: AEIOU.

We report five MCC patients diagnosed during the last 15 years in our Dermatology Department. We reviewed the literature and analyzed clinical features, treatment, and outcome. Our results coincide with previous publications: we found increased incidence; age and immunosuppression as predisposing factors; association with in situ squamous-cell carcinoma; tumor regression in one patient, and a mortality rate that depends on tumor size at the time of diagnosis (Dermatol Argent 2009; 15(6):428-433).

Key words: *Merkel cell carcinoma, primary cutaneous neuroendrocrine carcinoma.*

Introduction

Merkel cell carcinoma (MCC) is a rare primary skin tumor, highly aggressive both locally and in distant sites. It mainly affects the cephalic pole. Generally, it appears as a nodular, asymptomatic, rapidly expanding tumor, usually in patients over 50 years of age with photodamage and some type immunosuppression. This article reports five cases of patients with MCC diagnosed in the last 15 years in our Hospital. Clinical, histological and immunohistochemical features were assessed, as well as evolution and treatment.

Case series

Case 1

A 64-year-old male patient without relevant medical history, with skin phototype II and multiple actinic keratoses. He consulted on November 1996 for an asymptomatic round, raised, and erythematous tumor lesion with central ulceration and peripheral serosansanguineous crusts measuring 2.5 cm in diameter, located on posterosuperior area of left antehelix, of about one year evolution.

Histologically, the epidermis included an *in situ* squamous cell carcinoma (Bowen's disease) associated with an ill-defined adjacent dermal mass consisting of small, ovoid cells with scanty cytoplasm (**Figure 1**) expressing cytokeratin 20 in a paranuclear pattern. With electron microscopy, electron-dense

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granules were surrounded by an electron-lucid halo (**Figure 1**). Diagnosis was MCC.

Treatment. Tumor removal and graft on the resection area.

No local recurrences were identified after 7 years follow up.

Case 2

A 48-year-old female patient without relevant medical history, consulted in May 1998 for an asymptomatic, raised, spherical, brownish erythematous tumor lesion with irregular and ulcerated surface and defined borders, indurated, of about 3 cm in diameter, located on the medium third of the external aspect of the left leg, of a 5 months' evolution. Non-painful hard-to-elastic lymphadenopathies were identified at homolateral inguinal level.

The histopathological study revealed the presence of MCC: dermal proliferation of small, undifferentiated, round, and basophilic cells, with dusty chromatin and high mitotic count. These elements expressed cytokeratin 20 in a paranuclear pattern, neurofilaments and synaptophysin.

Supplementary studies showed increase of lactic dehydrogenase (LDH) and erythrosedimentation rate. Abdomen and pelvis computed axial tomography (CAT) showed homolateral inguinal lymphadenopathies.

Treatment. Complete resection and skin graft were performed, with subsequent homolateral inguinal node emptying, and metastases were identified in 2 of the 8 lymph nodes studied. She underwent 4 chemotherapy cycles with cisplatin and etoposide. A year after ending chemotherapy recurrence arose on the area adjacent to the graft and subsequent systemic tumor dissemination with lung metastases; she died shortly after.

Case 3

A 79-year-old female patient with history of low grade remitting non-Hodgkin lymphoma, type II diabetes and hypertension in treatment, consulted in February 2007 for an asymptomatic, warm and indurated erythematous plaque of a 3 months' evolution, with a dome-shaped, bright pink tumor lesion with surface telangiectasias, friable, of about 1 centimeter in diameter (**Figure 2**), located on left malar area. After a biopsy was performed, antibiotic treatment was indicated for 7 days, believing it to be a tumor bacterial superinfection.

Histology showed small dermal cells with scanty cytoplasm and positive immunohistochemical markers for cytokeratins 7 and 20, AE1AE3, chromogranin and synaptophysin, thus establishing diagnosis of MCC. Markers were negative for CD45 (leukocyte common antigen) and for B and T lymphoma. The patient showed clinical involution of the lesion (**Figure 2**). Excision with 2 cm in depth and with 3 cm wide margin was the elected treatment with no histological finding of tumor disease. At present (2 years follow up) the patient shows no sign of recurrence.

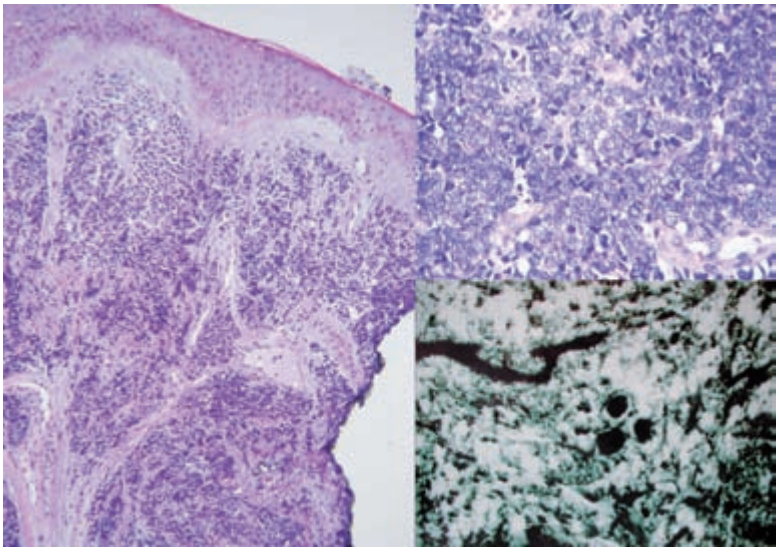

Figure 1. Left: *(10×) Poorly defined dermal mass.* ***Upper right:*** *(40×) Small ovoid cells with scanty cytoplasm.* ***Lower right:*** *(electron microscopy) Electron-dense granules surrounded by an electron-lucid halo.*

Case 4

A 77-year-old male patient with history of arterial hypertension and type II diabetes consulted in February 2008 for an asymptomatic, nodular, raised erythemato-purplish tumor lesion with hyperpigmented and ulcerated areas covered with serosanguineous crusts of 1 cm in diameter, friable, located on the forehead, of 3 a months' evolution (**Figure 3**). Histology showed small cell proliferation. Immunohistochemistry resulted positive for cytokeratin 20, synaptophysin (**Figure 4**), chromogranin and enolase.

Treatment. Lesion was removed with wide margins, and subsequent radiotherapy was instituted.

He continues with bimonthly controls, which are normal so far.

Case 5

An 89-year-old male patient consulting in April 2008 for an asymptomatic, round, raised tumor lesion with irregular crusty surface and defined borders, hard in consistency, located on left leg, of 4 months evolution (**Figure 5**).

Histopathology reported small dermal cells with scanty cytoplasm. Immunohistochemistry resulted positive for cytokeratin 20, chromogranin and synaptophysin. This information led to diagnosis of MCC.

Treatment. Surgical treatment was instituted, removing the lesion with 3 cm margins. Quarterly controls have been done since then.

Comments

Merkel cell carcinoma (MCC) is a rare malignant tumor described by Toker in 1972 as a trabecular carcinoma based on its infiltrating feature.[1]

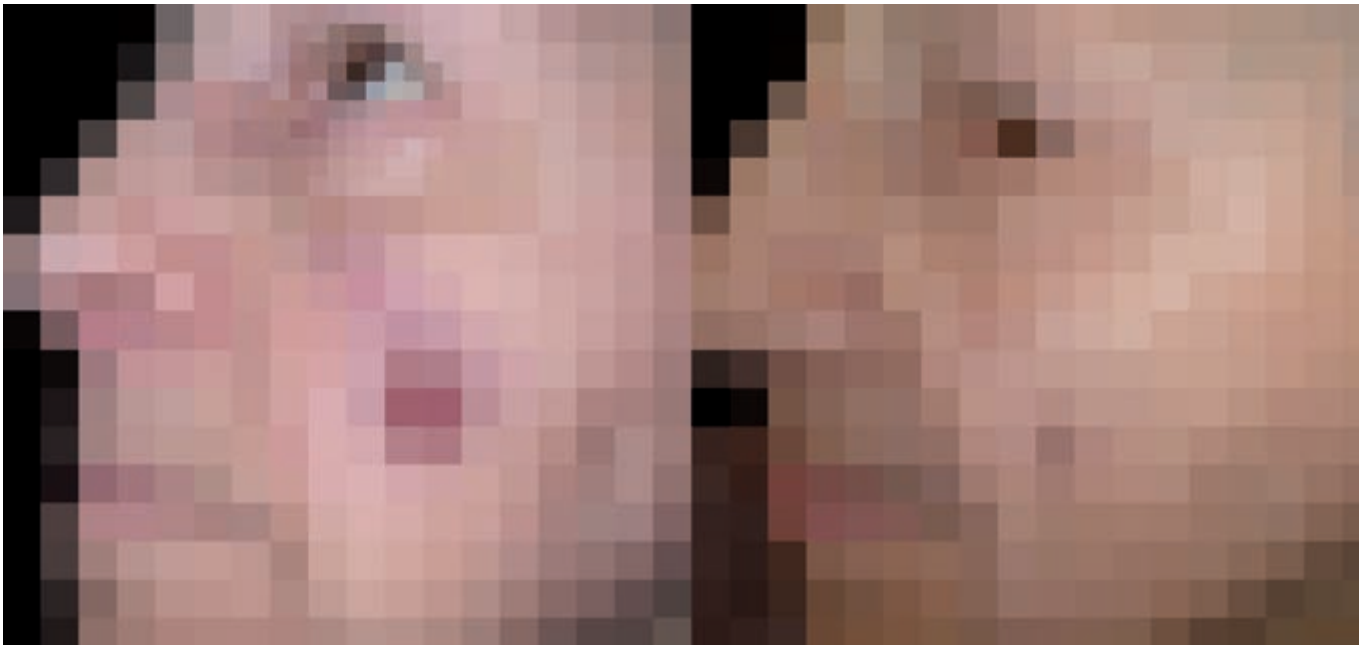

Figure 2. Left: *Dome-formed tumor lesion, bright pink in color, with telangiectasias.* ***Right:*** *Spontaneous tumoral resolution.*

In Argentina, the first case was described by Magnin et al., in 1982.[2] Its origin is unclear, since although ultrastructural findings of neurosecretory granules may lead to Merkel cells, and further to the neural crest,[3] others suggest an origin from epidermal pluripotent stem cell with high degree of differentiation into diverse phenotypes.[4] It seldom behaves as intraepidermal neoplasia.[5]

Although etiology is controversial, several factors contribute to its pathogenesis, including sun exposure, malignant epithelial tumors[6] psoriasis, arsenic exposure, chemotherapy immunosuppression,[7] HIV, chronic lymphocytic leukemia,[8] transplants and the presence of another neoplasia.

MCC may be associated with multiple skin tumors,[9] mainly squamous cell carcinoma, sharing many risk factors. Walsh reported 37 percent coexistence with invasive[10] and *in situ*[11] squamous-cell, as in case 1 patient.

Tumor incidence has trebled in the last 15 years (0.42 per 1,000,000 patients per year).[12] The increase in more than 1,000 cases per year in the United States has recently placed it as the second death-causing primary non-melanoma skin cancer.[13] The same trend appeared in our group of patients, since during the 15 assessed years, three patients have been diagnosed in the last 18-month period of time.

It is more frequent in patients older than 50 years, with slight prevalence of women. Photoexposed sites are most often involved: 65 percent of the cases involve head and neck; 18 percent involve upper extremities, and 13 percent involve lower extremities,

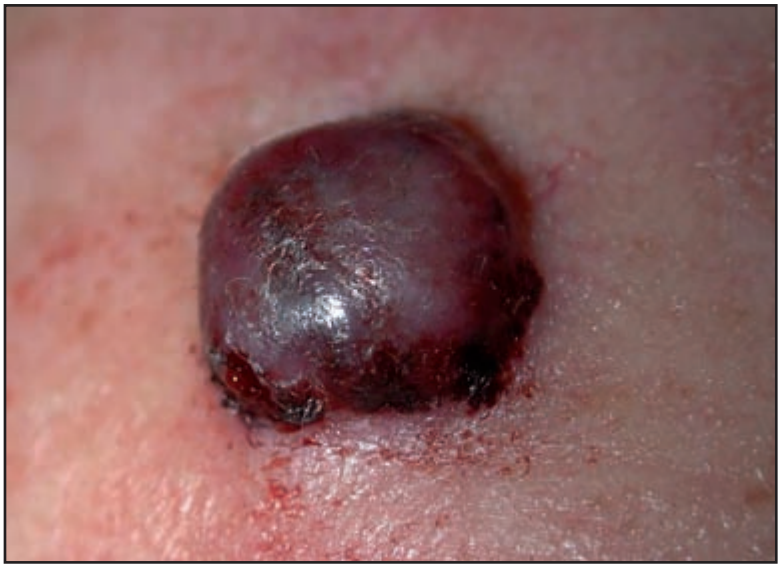

Figure 3. *Erythemato-purplish nodular tumor lesion on scalp with serosanguineous crusts.*

and less frequently trunk.[8] Involvement of other sites, such as vulva, penis, pharynx, and nasal and oral mucosa, has also been reported.[14]

Heath et al. described a prospective cohort study of 195 patients in which most (88 percent) were asymptomatic, rapidly expanding, and red or pink in color in 56 percent of the cases. Location was related to prior sun exposure in 81 percent of primary tumors, and most patients were older than 50 years old (90 percent). This group created an acronym clinically characterizing these tumors: **AEIOU** (**A**symptomatic; **E**xpanding rapidly; **I**mmunosuppression; **O**lder than 50 years; **U**VB-exposed).[14]

Our five patients showed at least three of the acronym clinical features. Taking into account epidemiological features,[15] the increase in incidence in the general population and the greater incidence in immunosuppressed and elderly patients were also observed in our series.

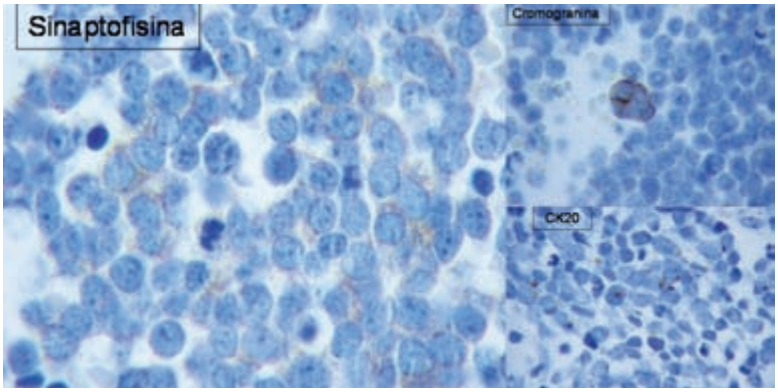

Figure 4. *Positive immunohistochemistry for cytokeratin 20, chromogranin and synaptophysin.*

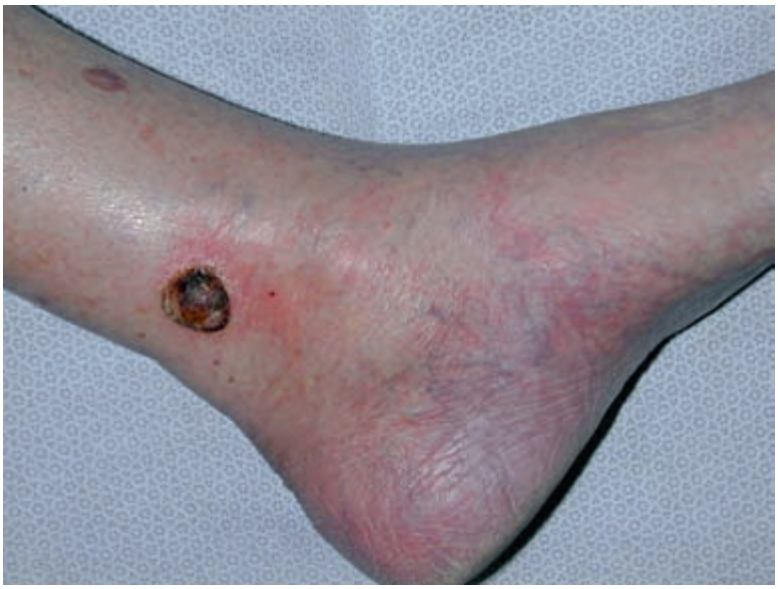

Figure 5. *Round and indurated tumor with irregular crusty surface on left leg.*

Feng et al. stated the hypothesis of a possible viral association, which was confirmed in 2008 by the detection of a polyomavirus viral transcription sequences. This virus is known as Merkel cell poliomavirus.[16]

The mortality rate is 33 percent in 3 years. Survival at 5 years is 75 percent, 59 percent, and 25 percent for localized, regional and distant forms, respectively.[13] Localized forms represent 49 percent of the cases.[17]

Histologically, MCC is characterized by proliferation of monomorphic cells with a large, round and regular nucleus, fine dispersed internal granular chromatin, multiple eccentric small nucleoli, and a high degree of mitosis. Cytoplasm is scanty and basophilic. Apoptosis is common.

Growth patterns are classified as: a) solid, b) diffuse, and c) trabecular.[18]

Immunohistochemistry results are positive for paranuclear cytokeratin 20, synaptophysin, chromogranin, specific enolase and neurofilaments, among others.[19] These techniques prompt differential diagnosis, mainly between MCC and cutaneous metastasis of small cell lung carcinoma. Although both tumors are positive for specific enolase and occasionally CD99 expressed in cytoplasm, MCC is negative for cytokeratin 7 (CK7). TTF1 (*transcriptional thyroid factor 1*) has also been described as a useful marker to differenciate MCC from small cell lung carcinoma.[20]

Other entities to be considered in differential diagnosis are: primary cutaneous lymphoma, which is negative for cytokeratins and positive to CD45 leukocyte common antigen and the corresponding B or T lymphocyte markers; small cell melanoma (negative for cytokeratins and positive to protein S-100); and primitive neuroectodermal tumor (negative to cytokeratins and positive to specific neuronal enolase and CD99, with membrane stain).

Electron microscopy shows small cells with scanty cytoplasm, electron-dense granules with a characteristic clear halo, and paranuclear intermediate filaments aggregates (cytokeratins).[21]

Early diagnosis is the best prognosis factor. Poor prognosis factors are: male gender, associated systemic diseases, location on trunk, head and neck, young age, local recurrence and location on legs;[22] these three last features coincide with patient 2 (the only patient with fatal outcome in our series). Histologically, a tumor larger than 5 mm with diffuse expansion pattern, dense lymphocyte infiltrate, high ki67+ mitosis index, large cell size, and vascular and lymphatic invasion are worst prognosis markers.[18]

The described treatments include, firstly surgical excision with 3 cm safety margins and 2 cm in depth,[23] and the sentinel lymph node technique.[24] Mohs micrographic surgery may be very useful, especially in cases requiring a good cosmetic outcome, and some authors report a better local-regional control than with traditional surgery. Even though radiotherapy (RT) has resulted in a reduction in the recurrences and metastases, thus increasing survival,[24,25] its use remains controversial.

A meta-analysis study of 1254 MCC cases published by Garneski et al. compared surgical treatment associated with RT vs. surgical treatment alone in a 5 years follow-up. It was concluded that surgical treatment with RT results in three-fold reduction of local and regional recurrences.[23]

Four of five reported cases were low risk tumor stages treated with surgical excision and followed by the Oncology Department; one case was further treated with radiotherapy. The only patient requiring chemotherapy had a poor outcome.

Currently, some authors believe that adjuvant chemotherapy as applied in case II is not a treatment of first choice, because it may increase morbility and mortality.[26]

MCC has increased incidence and poorer prognosis in relation to immune function impairment. It increases by 10 percent in patients with leukemia, solid organ transplant, and/or acquired immunodeficiency.[27]

Noteworthy is the tumoral autoregression in patient 3. Spontaneous regression of tumors and metastases of tumors excised by Mohs micrographic surgery have been described.[28] The mechanism is unknown,[29] but immunity may play a relevant role, and may be used in the near future as a therapeutic target.[30]

Conclusion

Although a rare tumor, MCC incidence is rising; thus, it is increasingly important to recognize the clinical, epidemiological and behavioral features of these tumors, as well as learning about the most adequate therapies and the most recent management guidelines to handle our patients, firstly by suspecting and establishing an early diagnosis (most important prognosis factor) and later by indicating the most suitable treatment.
Surgery with safety margins, biopsy of sentinel lymph node, and radiation therapy are useful in management of MCC treatment, but cannot always be applied because of patient comorbidities. A broader understanding of new associations, such as viral replication and immunity, and the mechanism of tumor regression may be the therapeutic target in a near future.

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