Merkel cell carcinoma: A case history

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Abstract

The authors make a presentation of a clinical case of a woman aged 80 years, admitted to the Medical Service 1 (SM-1) of the Hospital of S. Marcos de Braga (HSM-B) for study of lymph node metastasis of unknown primary carcinoma, which resulted in a diagnosis of "Merkel Cell Carcinoma". It gives a brief review is given of this type of neoplasia, which is relatively rare and little known.

Key words: skin cancer, Merkel cell carcinoma, metastasis of unknown primary carcinoma.

Introduction

Merkel cell carcinoma (MCC) is a relatively rare and little known primary cutaneous neoplasm. It originates in the skin, in the neuroendocrine cells, with features of epithelial differentiation.[1,2,3]

The diagnosis of a neuroendocrine carcinoma from the group of cutaneous neoplasms was the inevitable result of the emerging concept of "Diffuse Neuroendocrine System".

MCC was first described by Toker in 1972[2,3,4,5,6,7,8,9,10,11] as "trabecular cell carcinoma of the skin" and, later, by Tang and Toker, who demonstrated the neuroendocrine origin of the cells constituting this neoplasm, through electron microscopy. [12]

The Merkel cell, first identified by Fredrick Sigmund Merkel in 1875,[4,8,10,11] and its aspects of differentiation, which is both neuroendocrine and epithelial,[13] have led to considerable controversy regarding the origin of the cells. There are three possible hypotheses: from the neural crest with subsequent migration to the dermis and epidermis; from the diffuse neuroendocrine system; and from a primitive epidermal stem cell.[3,4]

This cell type is deeply located in the dermis,[10,12] (basal layer) and its function has yet to be determined.[6]

The literature places particular emphasis on the aggressive and potentially lethal nature of these tumors, particularly in the presence of diseases in advanced stages, for which the long-term prognosis is poor. [7]

Spontaneous regression of any malignant tumor is rare: for MCC however, although the overall prognosis is poor, four cases of spontaneous regression[1] are described in the literature. The mechanism is not definitively known, but Kayashima et al. propose the involvement of apoptosis and immunologically-mediated mechanisms as possible mechanisms in the evolution in some of the cases.[1,4]

Clinical Case

C.O.F., 80 years of age, female, Caucasian, married, born and living in Adaúfe, Braga, Portugal.

She was seen in the outpatient facility of the hospital in November 1989 due to left submandibular enlarged lymph nodes with about three months of evolution. Excisional biopsy was performed, for which the anatomopathological examination revealed metastasis from undifferentiated large cell carcinoma. The preliminary investigation was unable to identify the primary neoplasm.

On March 19, 1990, two new enlarged lymph nodes were detected in the right parotid region, and thus a surgical excision was performed. Histological examination revealed a ganglion infiltrated by small and large lymphocytes, suggesting lymphoma or metastatic, undifferentiated carcinoma. The tests carried out, including analytical studies, upper and lower gastrointestinal endoscopies, and abdominal echography, and the Ear, Nose and Throat examination, were

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unsuccessful. The patient was referred to Oncology Group Consultation (COG) for decision and final guidance. It was suggested that patient be admitted to Internal Medicine for characterization of the primary tumor. She was admitted to the Internal Medicine Service 1 of the HSM-B on 13th June 1990.

The patient had a history of cutaneous lesion on the nasal dorsum, having been observed in the Dermatological outpatient department of the HSM-Braga in October 1988, where she underwent complete surgical excision of a probable "basalioma".

There was one death of a daughter of breast neoplasm in the family history.

Subjectively, the patient was in good health, without any symptoms associated with the different body systems.

On objective examination, the patient was conscious, cooperative and oriented, with a reasonable state of nutrition. Blood pressure was 150/90 mmHg, heart rate 72 beats/min, with good, rhythmic and regular heartbeat, respiratory rate 16 breaths/min and axillary temperature 36.5ºC.

She had a hard, deep, painless swelling of approximately 6x4cm diameter in the right submaxillary region.

She also had a nodular, ulcerated cutaneous lesion of about 1 cm diameter in the frontal region.

During her staying in the hospital, she underwent a surgical excision of the cutaneous lesion in the frontal region. Histological examination revealed a "basosquamous carcinoma with adenoid areas" (complete excision).

The examinations performed included CT scan of the cervical spine, which revealed a large mass of about 4 cm diameter in the right submaxillary region, consistent with a group of enlarged lymph nodes (*Fig. 1*). Chest and pelvic abdominal CT scans revealed no significant changes.

On 19th July 1990, a block excision of the cervical tumor was performed, which was identified in the anatomopathological examination as "lymph node metastasis of undifferentiated small cell carcinoma." For better histological definition, immunocytochemistry was subsequently carried after the patient was discharged. The final diagnosis was lymph node metastasis from MCC.

The case was referred to the COG team, who decided to observe the patient in a follow-up, without any additional therapy, in view of the apparent control of the disease.

On 27th January 1992, the patient was admitted to the ER of the HSM-Braga with skull fracture and bruising in the right parietal lobe. In the neurological examination, despite presenting aphasia and conjugate right-eye deviation, the patient was alert, but her condition was not improved. She was therefore readmitted to the SM-1 of the HSM-B and underwent a delayed brain CT scan. The CT scan revealed marked hypodensity of the white matter of the cerebral hemispheres, and some cortical hyperdensity in the left temporal and right frontal poles, consistent with the diagnosis of multiple metastatic foci (*Fig. 2*).

She started taking anticonvulsants and corticotherapy and, in February 1992, she was discharged, in a reasonable state of consciousness, with no focal neurological impairment, and without conditions to aggressively fight the neoplasm.

Finally, on 6th March of that same year, she was again readmitted to our hospital with respiratory failure due to "bronchopneumonia", of which she died two days later.

Comments

MCC is, among the primary neoplasms of the skin in the elderly, the one that most often occurs in areas of skin exposed to the sun.[1] Its actual incidence is unknown, but it typically occurs in the elderly (over 65 years), although there are reported cases of occurrence in patients aged 7 to 95 years.[3] It has also been reported in young adults and patients with congenital ectodermal dysplasia. This neoplasm affects mostly Caucasian individuals, and no clear difference in incidence between the sexes has been found.[3,11] MCC occurs mostly in the skin of head and neck (50%);[3,4,6,10,11] in approximately 40% of the cases it affects the extremities,[11] and in less than 10% it affects the trunk and mucosa.[3] Very few cases of multiple MCC have been reported.

Its typical appearance is a single nodular lesion, with a red or purple, shiny surface, sometimes accompanied by telangiectasias.[3,6,11,14] Ulceration is rare and is observed in less than 10% of cases, and most tumors measure less than 2 cm in diameter. The tumor may extend into the hypodermis, subcutaneous fat, and subjacent skeletal muscle, but it rarely invades the epidermis.[2,3,6,10]

Although under optical microscopy the histological pattern may suggest the diagnosis, there is an

evident risk of confusion with other poorly differentiated small cell tumors, therefore it is recommended to complement this diagnostic method with electron microscopy and/or immunocytochemistry.[9]

The tumor cells of MCC are ultra-structurally similar to normal Merkel cells.[14] They have lobed nuclei with multiple small nucleoli, and characteristically, dense, membrane-delimited[10] cytoplasmic granules appear[9,11,14] of about 80 to 120 nm in diameter, and paranuclear aggregates of intermediate filaments.[3,8] This is usually a tumor of rounded and uniform cells, with a well-defined, oval or rounded, sometimes indented nucleus, and variable cytoplasm [10] (*Fig. 3*). The mitotic index is usually high, suggesting necrotic spots and cellular apoptosis. Lymphatic and vascular invasions, and peripheral infiltration by lymphocytes and plasma cells, are common findings. [1,10,14]

Histologically, three basic structural types are defined [2,3] (*Table I*): "Trabecular or classic," "intermediate cell" and "small cell".

The definitive diagnosis of MCC can be further confirmed by the presence of characteristic epithelial and neuroendocrine markers,[14] particularly positivity for low molecular weight cytokeratins (*Fig. 4*), neurofilament proteins (in a paranuclear position), neuronspecific enolase (*Fig. 5*), chromogranin (secretory proteins from dense granules) and synaptophysin (neuroendocrine vesicular membrane protein), and negativity for protein S100 and common leukocyte antigen.[2,3,6,7] In a small minority of cases, some neuropeptides were also detected, specifically: VIP, calcitonin, ACTH, gastrin and somatostatin.[3]

Having diagnosed MCC, it is then necessary to perform a general clinical examination, with complete patient history and physical examination, which should always include a complete skin examination, and palpation of ganglia, liver and spleen.

Likewise, due to the implications of expansion of the disease on the therapeutic strategy, a complete blood count, liver function tests, plain chest radiography and abdominal echography should complete the investigation.

A CT scan should only be requested when there are high-risk lesions or suspected distant metastasis. [6,7]

MCC has an aggressive biological behavior and a high incidence of local recurrences (more than 30% of the cases occur during the first year after excision of the lesion), regional recurrences (40-70%) and systemic spread (25-40%, usually detected in the first 2 years of the disease).[3,6,9] No reliable data exist for five-year survival rates, but some authors believe it to be less than 50%.[3] However, the average two and three year survival rates for males and females are: 58% and 79%, and 36% and 68%, respectively.[1,8]

TABLE I

Histological Types of Merkel Cell Carcinoma

Histological Types	Characteristics
Trabecular or classic	1/4 of all cases Most differentiated type Network of trabeculae separated by bands of connective tissue Occasional pseudo-rosettes or pseudo-glandular formations
Intermediate cell	Compact nests of intermediate size cells Peripheral trabecular pattern Necrosis of isolated cells or small necrotic spots
Small cell	Less frequent Harder to diagnose Small cells sometimes mixed with intermediate cells Irregular, hyperchromatic nuclei, and scarce cytoplasm

Some clinical and histopathological indicators correlate with a worse diagnosis:[3]

- Tumor > 2 cm.
- Location in the head and neck.
- Metastasis at the time of presentation.
- Evidence of lymphatic and/or vascular invasion.
- Small cell histological pattern.
- Mitotic index > 10/ high power field.

The most common sites with metastasis are the liver, lungs, brain, bones and skin, although metastasis have been described in almost all organs.[10]

Given the rarity of these tumors and the relatively short follow-up experience, the ideal approach and handling have not yet been clearly defined.

Due to its aggressive behavior and capacity for regional and distant metastasis, early recognition and appropriate initial excision of the lesion are fundamental, with safety margins of 2.5 to 3 cm.[3,4,8,11,13]

Many authors recommend an enlarged surgical re-

TABLE II

Guidelines for treating patients with MCC

Group/Definition	Primary treatment	Alternative treatment
Localized disease (limited to the site of the primary lesion)	Surgical excision with margins of 2.5-3 cm Adjuvant radiation (a)	Radiation as primary treatment (b) Others (c)
Regional disease (invasion of regional ganglia) or Local recurrent disease	Surgical excision + dissection of primary drainage lymph nodes + supplementary radiation (d)	Chemotherapy? (e) Others (c)
Systemic disease (distant metastasis)	Chemotherapy (f)	Combined surgery + radiation + chemotherapy

a) In the following situations: surgical excision with margins lower than the expected safety margins; when angiolymphatic invasion is evident
b) In patients with unresectable tumor, or neoplasm located on vital structures (e.g., eyes)
c) Experimental therapies: Intralesional tumor necrosis factor (TNF); intralesional interferon alpha-2b.
d) According to the regimen: total dose of 4000-5000 cGy in 20-25 sessions over a period of 4-5 weeks.
e) According to some authors, its early use is indicated for: Neoplasm composed of <<small cells>>; lymph node compromise at diagnosis; extensive and unresectable local disease; recurrent disease and systemic disease.
f) Regimens equivalent to those used in the treatment of Small Cell Lung Cancer.

section and emptying of the regional lymph nodes.[2]

Its sensitivity to a wide variety of chemotherapy agents[7,8,10,12] is also well documented, as well as its radiosensitivity,[4,7] showing that prophylactic irradiation of the primary lesion site[3,4] and regional lymph nodes[7,11] are beneficial. Nonetheless, even though postoperative radiation could lead to improved control of the disease loco-regionally, it did not solve the serious problem of distant metastasis.

Inevitably, assuming some uncertainty regarding the correct treatment regimens to be used, it is now possible, by classifying patients in three large groups,[3] to define some consensual guidelines in order to optimize treatment. These are summarized in *Table II*.

The different histological types are related, certainly, to the same pathological process, yet they have received different terminology, and we believe that the initially excised lesion corresponded to the primary cutaneous MCC. Despite the apparent control of the local disease, metastasis started to develop about two years later in one of the exclusive sites.

In retrospect, we believe the approach chosen for the initial condition of the patient was clearly insufficient. Given the options available, some kind of adjuvant therapy – radiation or chemotherapy - should have been used to complement the surgical dissection, as the patient had a reasonable performance status.

In conclusion, we can state that the Merkel cell carcinoma, an uncommon but aggressive skin tumor, is often underdiagnosed and, therefore, inadequately treated. ■

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