Merkel cell carcinoma of the head and neck: Report of seven cases

Ramón Luaces Rey [1], Javier Fernández Alba [2], Roberto Martín [3], Álvaro García Rozado [1], Sabela Paredela [4], Olga Robles [5], José Luís López Cedrún [1]

(1) Department of Oral and Maxillofacial Surgery. Juan Canalejo Hospital. A Coruña.
(2) Department of Oral and Maxillofacial Surgery. Guadalajara Universitary Hospital.
(3) Department of Oral and Maxillofacial Surgery. Toledo Hospital.
(4) Department of Dermatology. Juan Canalejo Hospital. A Coruña.
(5) Department of Pathological Anatomy. Juan Canalejo Hospital. A Coruña. Spain

Correspondence:
Dr. Ramón Luaces Rey
Department of Oral and Maxillofacial Surgery
Juan Canalejo Hospital
As Xubias s/n, A Coruña. Spain
E-mail: rluarey@canalejo.org

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Abstract

Merkel cell carcinoma is a rare and aggressive primary cutaneous neoplasm. Clinically it is characterized by innocuous appearance, as a fast growing asymptomatic nodule or plaque. Head and neck are the most common sites of presentation (50%). The treatment is based on local surgery completed with cervical lymph node dissection, radiotherapy, chemotherapy and other treatments depending on the staging. Sentinel lymph biopsy seems to be useful for its treatment. Tumour staging is the only prognostic factor related to overall survival. Prognosis is very poor due to the high incidence of loco-regional recurrence and metastases. Seven cases of Merkel cell carcinoma of the head and neck are reported. These were treated in our Department over the last two and a half years. A literature review was made.

Key words: *Merkel cell carcinoma/sentinel node biopsy/facial oncology.*

Introduction

Merkel cell carcinoma (MCC) is an uncommon type of skin cancer, described for the first time in 1972 by Toker. Incidence ranges from 0´2 to 0´4 cases /100.000 people/ year.

These tumours appear in the 7th and 8th decade of life. There is almost no gender difference (1). Nevertheless there is a marked difference between races. Incidence is twenty times greater in whites compared to blacks (1). This explains sun exposure as a risk factor. Another risk factor is immunodepression.

The clinical appearance is not specific. It grows rapidly to a painless nodule or indurated plaque. Electron microscopy and immunohistochemistry are very helpful. MCC is very aggressive, presenting with high grade local recurrence, with regional lymph nodes and metastases (2, 3).

Treatment is based on either surgery alone or combined oncological therapies. The aim of this article is to present seven cases of an infrequent pathology of the head and neck treated in our Department.

Material and Methods

Seven patients with Merkel Cell Carcinoma (MCC) of the head and neck were treated during the period 2004-2006 at the Department of Oral and Maxillofacial Surgery, Juan Canalejo University Hospital, La Coruña, Spain (Table-1)

The first case was diagnosed as an MCC involving right lacrimal gland (figure 1).The treatment was local excision. Follow-up was done for a year and a half, until the patient died from unrelated causes (ischemic heart disease).

The second case was diagnosed as MCC localized in the right pre-auricular area (figure 2). Aggressive wide local

Table 1. Patients´ characteristics.

	Sex	Age	Lession	Place	TNM	Treatment	Evolution
Case 1	M	79	3cm painless mass	Right lacrimal gland	II (T2N0M0)	Local surgery	Died for unconnected cause 1 year and a half after surgery
Case 2	F	82	1cm exofitic lession	Right preauricular	III (pT1N1M0)	Local Surgery+neck dissection+radiotherapy	Metastases 7 months after surgery (died in 1 month)
Case 3	F	82	1 cm nodule	Left helix	I (T1N0M0)	Excisional biopsy+Radiotherapy	Cervical recurrence 7 months after surgery:local surgery+neck dissection+radiotherapy 16 months free
Case 4	F	55	1 cm nodule	Right supraciliar	I (T1N0M0)	Local surgery+ sentinel node biopsy (negative)	1 year and a half free of recurrence
Case 5	F	62	0,5 cm subdermal	Right malar	I (T1N0M0)	Local surgery+ sentinel node biopsy (negative)	9 months free of recurrence
Case 6	M	88	1 cm	Right preauricular	I (T1N0M0)	Family rejected treatment	No monitoring
Case 7	F	83	1cm	Upper left eyelid	I (T1N0M0)	Excisional biopsy+ follow up	3 months free of recurrence

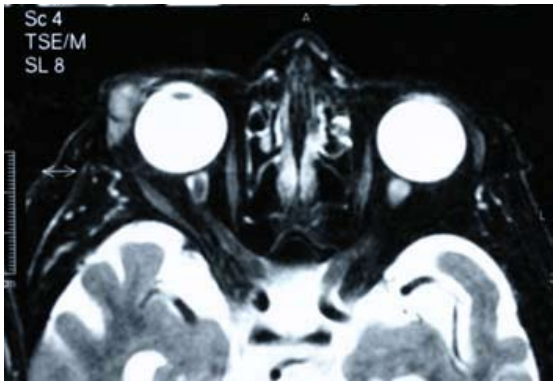

Fig. 1. Case 1: MRI.

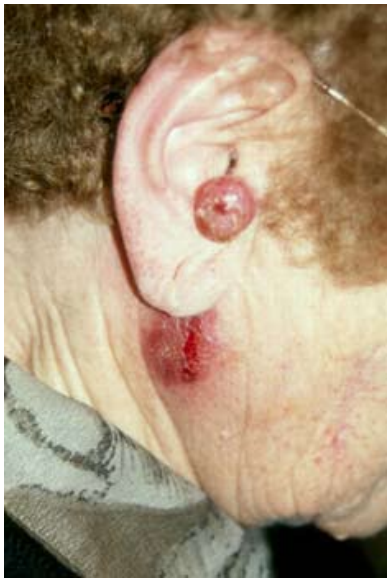

Fig. 2. Case 2: Before surgery.

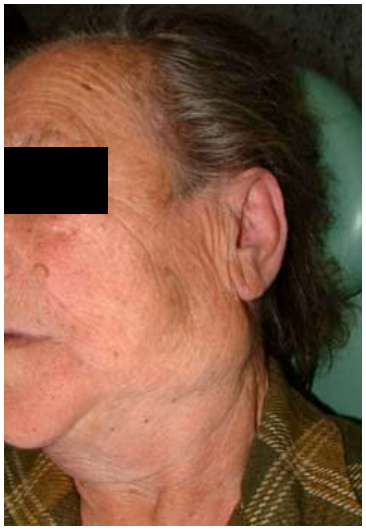

Fig. 3. Case 3: Cervical recurrence (before surgery).

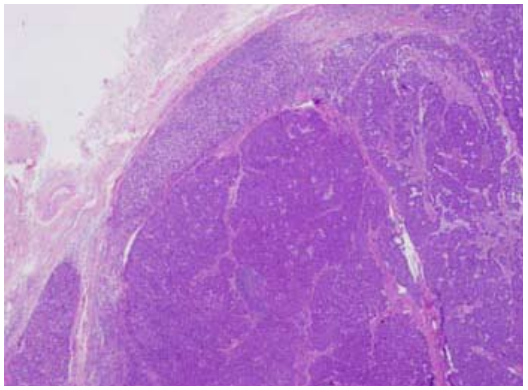

Fig. 4. AP study: lymph nodes affected metastases (H&E X10).

Table 2. Evidence in favour and against possible origin of MCC in cutaneous Merkel cells

MERKEL CELLS ARE THE ORIGIN OF MCC	MERKEL CELLS ARE NOT THE ORIGIN OF MCC
Morfologic similarity	Merkel cells are in epidermis but MCC is originated in dermis and subcutaneous tissue
Merkel cell share celular markers with tumoral cells (neurone-specific enolase…)	They don´t share all the celular markers
	Merkel cells don´t have neuroprotein filaments (unlike tumoral cells)

MCC: Merkel cell carcinoma

excision and right supra-omohyoid neck dissection was the chosen treatment. One of the seven lymph nodes examined was affected, with bad prognosis (high mitotic index and lymphocytic infiltration). The treatment was completed with adjuvant radiotherapy to the primary site. It was classified as Stage III (pT1 N1 M0). Seven months after the surgery she developed supra-sternal metastases, and on the abdominal CT-can hepatic an ovarian metastases were shown. The patient died eight months after the surgery.

The third case was diagnosed as MCC on the left helix area. Radiotherapy was chosen (30 Gy Cobalt60) after the excisional biopsy. A left submandibular metastatic lymphadenopathy measuring 3 by 4 cm was discovered seven months after surgery, and also a 2 cm retro-auricular lymph node attached to the skin (figure 3). The treatment was wide local excision of the primary lesion, superficial parotidectomy and radical neck dissection. Four of the 25 lymph nodes examined were affected (figure 4). It was classified as Stage IV (T1 N2 M0) and treatment was completed with radiotherapy (50 Gy Cobalt60). The patient has been free from recurrence 16 months after surgery.

The fourth and fifth cases had MCC in Stage I (T1 N0 M0). The treatment in both was wide local excision and sentinel lymph node biopsy, which were negative. The patients are under outpatient monitoring, free from recurrence respectively one and a half years and 9 months after surgery.

The sixth case was diagnosed as MCC in the right pre-auricular area. The initial therapy plan was to perform a wide local excision and a sentinel node biopsy. The family rejected treatment because of the patient's general condition, suffering from senile dementia. There has been no follow-up of this patient.

The seventh case was diagnosed with MCC in another hospital and was sent to our Department six months later. No therapy was started, based on the patient's age, medical history and the fact that there had been no recurrence.

Discussion

MCC is a malignant neuro-endocrine dermal neoplasm (4). Nevertheless, there is no agreement about its etiology. There is evidence both in favour and against its possible origin in cutaneous Merkel cells (Table-2). Some authors defend its origin on neuro-endocrine dermal cells, or in epidermal stem cells in the basal layer of the epidermis capable of differentiation along either lineage (5, 6). This is based on the co-existence of MCC with other dermal neoplasm (squamous cell carcinoma, basal cell carcinoma), and the presence of glandular or epidermal differentiation in the interior of the tumour (7).

Sun exposure (1, 8) and immunodepression (8) are the most significant risk factors. The high incidence in whites compared with blacks and the typical presence in sun damaged skin (9) supports this theory. The co-existence of this skin tumour with other dermal neoplasia related with ultraviolet radiation has been reported (5, 6).This suggests the appearance of genetic mutations that could lead to these lesions.

Incidence is elevated in immunodepressed patients. This conclusion being reached based on studies of the incidence of Merkel cell carcinoma in patients with heart or kidney transplantation (8), patients under immunosuppressant treatment , patients infected with HIV (10), and patients affected by different hematological neoplasia and other malignant tumors (11).

In spite of the aggressiveness of MCC, the characteristic innocuous appearance leads to diagnosis in advanced stages. It appears in the skin as a solitary nodule or as an indurated plaque. Generally red or deep purple, the surface is shiny with telangiectasias and the epidermis is intact. Typically it is asymptomatic, fast growing in weeks or months, and a size smaller than 2 cm diameter. More than a half of these tumours occur in the head and neck region (5, 9).

Anatomopathological study is the basis of the diagnosis. MCC locates in the dermis and grows toward subcutaneous tissue, with a tendency to infiltrate vascular and lymphatic vessels (12). Epidermal surface is unusually affected. It is formed by uniformly sized basophilic cells, with round nuclei and small nucleoli (12). The presence of areas of focal necrosis, mitotic activity and lymphocytic infiltration are very common. There are basically three histological patterns: The first one is the trabecular type, the second one is formed by sheets (?) and clusters and the third is the intermediate type (the most common one).

Presence of immunoreactivity to a few epithelial markers

(epithelial cytokeratin 7, 8, 18 y 20, CEA, desmoplakin…), neuroendocrine markers (neuron-specific enolase, chromogranin-A, synaptofisin…), neurofilaments (neurofilament-L), among others, is useful to the diagnosis (4) (figure 5). Some authors defend that the characteristic cytokeratin and neurofilaments dye patterns are very important for the diagnosis.

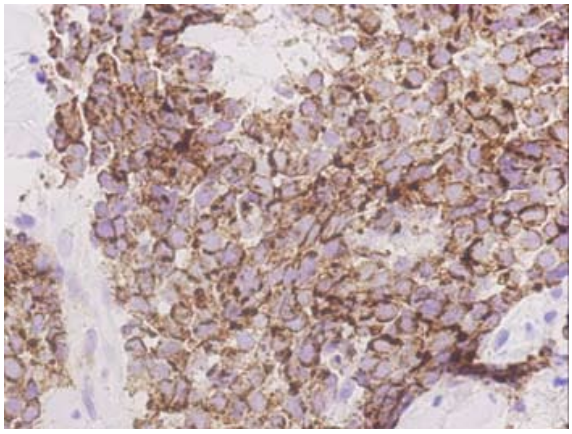

Fig. 5. Immunoreactivity to chromogranin-A (X10).

Electron microscopy plays a significant role in the diagnosis of MCC for some authors, because of the possibility of recognize peripheral neurosecretory granules and neurofilaments (4).

The non-specific characteristics of this neoplasm, lead to a lengthy differential diagnosis, which among others includes amelanotic melanoma, neuroblastoma and dermal metastases of inner neuroendocrine tumours such as metastatic oat cell carcinoma (4, 12, 13).

No single standard of care exists for the treatment of this aggressive tumour. However it's accepted that the basis is surgery, completed if necessary with other therapies (1, 9). Wide local excision is very important, with large free-margin recommended (2-3 cm.) (14, 15). Moh´s micrographic surgery could be useful, because of the better local control, avoiding in some cases postexcision irradiation.

Prophylactic neck dissections is controversial, and doesn't seem to be indicated (11). Lymphadenectomy is recommended in case of regional nodes metastases (cervical palpable nodes, or on CT scan of the neck), before radiation therapy. Neck dissection should be indicated in the case of positive result of sentinel lymph node biopsy (1, 2, 3, 13, 16-18), although this technique in MCC is not so extended as in oral squamous cell carcinoma (19).

Although radiotherapy doesn't increase overall survival (20), it increases the time free of recurrence. It's indicated as a prophylaxis in order to avoid recurrence and regional lymph nodes metastases (1, 8, 20). Therapeutic useful includes regional nodes metastases in cases where surgery should be avoided (20), in patients with bad prognosis histological findings (several lymphatic nodes invasion, extracapsular dissemination, or more mitoses per high-power field) (13). Other utility are occasional tumour persistence, or as palliation in disseminated disease (20).

MCC is sensitive to some chemotherapeutic agents. The most commonly used agents are cisplatin, etoposide and cyclophosphamide. But their use is restricted to metastatic disease or local recurrence (13). Complete remission is obtained infrequently on this way. Chemotherarapy doesn't increase the overall survival (15, 18).There are hopes in recent therapies on development yet, like intratumoral injection of Tumoral Necrosis Factor (TNF-α), or local hyperthermic perfusion of chemotherapy agents, but there is no conclusive evidence.

Tumour stage according to TNM Stage is the most important prognosis factor (5, 10). It is the only one related with overall survival in fact (1). In order to determinate the stage, is necessary to establish the total extension of the lesion by imaging techniques (CT scan, MNR, gammagraphy)

There are other prognosis factors that lack of studies to check their predictive meaning. On this way, a smaller cellular size, increased mitotic activity, immunosuppressor treatments, mucosal localization, presence of other neoplasm, female gender and advanced ages are associated to a worse evolution (1, 8, 14).

MCC is a deadly disease with a poor chance for survival. In the moment of the diagnosis or during the monitoring, 50-79% develops regional lymph nodes or distant metastases (30-40%) (1). It can even appear as a metastatic disease of an unknown primary tumour. Most frequent distant metastases are lymph nodes (60%), skin (30%), lungs (23%), CNS (18%), bone (15%) and liver. Survival rate varies depending on the authors, but is approximately 50% in 3 years (1), with local recurrence of 30% in Stage I-II in the first year (1, 5). Regional lymph node recurrence is 50% after two years (5) and about 40% develop metastases. Following treatment, patients are monitored monthly for six months, every three months for the next two years and biannually thereafter.

Conclusion

Merkel cell carcinoma is a very aggressive neoplasm, maybe due to not being diagnosed early on. Its mortality rate exceeds that of melanoma.

The current treatment of Merkel cell carcinoma is local surgery and regional oncological therapy. Sentinel lymph node biopsy may provide an accurate and less morbidity alternative to neck dissection for the treatment and staging of regional occult neck disease in Merkel cell carcinoma. Ultraviolet radiation is the main risk factor described so the only known prophylaxis is photoprotection.

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