BRIEF COMMUNICATION

Merkel Cell Carcinoma: A Presentation of 5 Cases and a Review of the Literature

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Abstract Merkel cell carcinoma is an unusual, aggressive skin tumour, with a tendency to recur after its surgical extirpation. Five cases of tumours in the cervicofacial region seen at our Centre in the last 5 years are presented, along with a review of the literature, focusing on its etiopathogenesis, approach and treatment.

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PALABRAS CLAVE
Carcinoma de células de Merkel; Carcinoma trabecular; Apudoma cutáneo; Carcinoma neuroendocrino epitelial; Carcinoma primitivo de células pequeñas de la piel

Carcinoma de células de Merkel: presentación de 5 casos y revisión de la literatura

Resumen El carcinoma de células de Merkel es un raro tumor neuroendocrino de localización epitelial, muy poco frecuente, agresivo y con tendencia a la recurrencia después de la extirpación quirúrgica. Presentamos 5 casos de tumores localizados en la región cérvico-facial en los últimos 5 años en nuestro servicio. Se revisa la etiopatogenia, abordaje y tratamiento de este tumor en la literatura médica.

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Introduction

Merkel cell carcinoma (MCC) is a primary cutaneous tumour of neuroendocrine type. It is rare, with a poor prognosis and a low survival rate. It is prone to lymph node and vascular involvement, related in both cases to a high rate of locoregional recurrence within the first year of tumour removal.\(^1\) It generally occurs in elderly people over 65 years of age, although there have been cases reported in young patients who were carriers of ectodermic congenital dysplasia syndrome.\(^2\) It preferably affects areas exposed to the sun: 55% in the head and neck, 40% in the limbs and 5% in the trunk.\(^3\) In almost one third of cases, this tumour is associated with other skin neoplasms such as Bowen carcinomas, basal cell or squamous cell carcinomas.\(^4\)

It may appear as a secondary malignancy in patients with immune disorders of different aetiologies: chronic lymphocytic leukaemia, B-cell lymphoma and myeloma; it also appears in patients who have received organ transplants or are in prolonged treatment with immunosuppressors.\(^5\) Aggressiveness and mortality are even higher in such patients.

Its anatomical–pathological diagnosis is complicated, as it can easily be confused with cutaneous metastases of other tumours: Ewing’s sarcoma, small cell tumour of the lung (oat cell carcinoma) or neuroblastoma. Its accurate diagnosis requires the use of electron microscopy and immunohistochemistry.\(^6\)

Merkel cell carcinoma was first described by Toker in 1972, under the name trabecular skin carcinoma owing to its histological characteristics.\(^2\) Subsequently, this tumour has received different names: Merkel cell cutaneous neoplasm, cutaneous apudoma, neuroendocrine carcinoma of the skin, small cell primary carcinoma of the skin, primary undifferentiated carcinoma of the skin, skin cell carcinoma of unknown obscure origin (Murky cell carcinoma), primitive small cell carcinoma of the skin with endocrine differentiation.\(^3\) The origin of this tumour is still unknown. Recent studies have found the presence of cytogenetic abnormalities in different chromosomes.\(^7\) Van Gele et al.\(^7\) found the existence of a mutation in the short arm of chromosome 10 in a large number of cases, which would result in the inactivation of PTEN (tumour suppressor gene).

We performed a retrospective longitudinal descriptive study of cases treated at our department over the past 5 years.

Material and Methods

We carried out a retrospective study of patients diagnosed with MCC in the last 5 years in our service. We performed a joint search at the ENT and dermatology services, seeking patients diagnosed solely with MCC in the cervical–cephalic region. We excluded 2 cases of patients with cases of multiple MCC in different locations who presented tumours in the cervical region in relation to metastasis; one case was of thoracic MCC and another case, of primary carcinoma in the region of the hand.

Results

We identified 5 consecutive cases of patients diagnosed with MCC, whose characteristics are described in Table 1.

The lesions presented were located in the auricular pavilion (3 patients in total) and frontal region (1 patient) and the cheek (1 patient). The typical appearance of the tumour is a nodular erythematous lesion, which may appear ulcerated (Fig. 1). Fig. 2 shows an example of the typical histological appearance.

All patients had a history of multiple previous skin cancers. Diagnosis found distant metastases in 40% of cases. Tumour recurrence took place in 60% of cases and was always early (<1 year). In 66.7%, there was only locoregional recurrence (2 cases) and metastasis was distant in 33.3% (1 case).

Discussion

This carcinoma appears as a solitary nodule, painful and rapidly growing, or as an indurated redish-purple plaque with superficial telangiectasias. Ulceration and bleeding are frequent and may be accompanied by satellite lymphadenopathies. The tumour generally occurs in patients with a history of multiple skin tumours, as evidenced in the literature reviewed and the cases presented. Cervical–cephalic location has a better prognosis than lesions affecting the trunk or limbs.\(^3\) It tends to appear after the sixth decade of life, as evidenced by our cases, with an average age of 79.6±2 years. The male/female ratio is 1.5/1, and it is more common in areas exposed to the sun or in areas exposed to irritating substances.\(^8\) In fact, all patients in our series presented some history of epithelial tumour.

Merkel cells are located in the basal layer of the epidermis. Electron microscopy has demonstrated the presence of dense granules of neuroendocrine type, as well as mechanoreceptors.\(^9\) These cells are a cellular subpopulation derived from the neural crest that are associated with nerve endings and act as mechanoreceptors; exocytosis of neurotransmitters takes place after a mechanical stimulus.\(^9\) They belong to the diffuse neuroendocrine system (DNES).

The clinical differential diagnosis should principally include basal cell carcinoma, squamous cell carcinoma, amelanotic melanoma, keratoacanthoma, lymphoma, fungal mycosis, cutaneous metastasis of small cell lung cancer (oat cell carcinoma), extraskeletal Ewing sarcoma, neuroblastoma, plasmacytoma, medullary thyroid carcinoma, anaplastic carcinoma, eccrine cell carcinoma and histiocytosis X. Definitive diagnosis is carried out by clinical–pathological correlation but it is important to confirm it by electron microscopy and immunohistochemistry.\(^10\)

The histological patterns can be of 3 types: trabecular or classic, intermediate cellular, or with small-cell pattern.\(^12\) The most common is the intermediate, characterised by the existence of a circular arrangement in nests or rosettes of intermediate cells, either in solid clusters or with a conjunctive centre, accompanied by a peripheral trabecular pattern. The small-cell pattern type has a worse prognosis and shows a diffuse infiltrate of small neoplastic cells in sheets. Electron microscopy shows ultrastructural characteristics of neoplastic cells, such as a round or oval nucleus.
<table>
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<tr>
<th>Patient</th>
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<th>Complementary MCC Studies</th>
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Figure 1  (A) MCC in right pretragal region associated with frontal tumour (squamous cell carcinoma). The patient refused treatment for epithelial lesions at this point. (B) State of the tumour 2 months after the first image; the tumour had doubled in size and a CT scan had verified its extension in depth, until it affected the entire parotid region. The larvae of myiasis could be observed. The tumour had a foul odour. In such circumstances, the patient did agree to the proposed surgery.

with one or two deep notches, as well as a small eccentric nucleolus with dispersed chromatin and free polyribosomes. Their cytoplasm characteristically presents granulations or round vesicles, 210 μm in diameter, with an electron-dense area inside separated by an electron-lucid one, and which are scattered or aggregated at one pole of the cytoplasm. They also present a dense paranuclear band corresponding to intermediate filaments known as paranuclear fibrous bodies.12

Immunohistochemistry is necessary to confirm the presumptive diagnosis. This process uses neuron-specific enolase (NSE) and CKE1-CKAE3 (specific epithelial markers), CK20 (the most specific; positive in 95% of MCC), chromogranin, synaptophysin, epithelial membrane antigen (EMA) or desmoplakin.10 The following are negative: common leukocyte antigen, used for differential diagnosis with lymphoma and leukaemia; S100, which rules out melanoma and fibrous histiocytoma. A minority of neoplasms may be associated with the tissue presence of neuropeptides, including calcitonin, ACTH, bombesin, gastrin, met-enkephalin and somatostatin. Both CK20 and thyroid transcription factor 1 (TFF-1) differentiate Merkel carcinoma from small cell lung carcinoma (oat cell carcinoma) or extrapulmonary carcinoma.13

Figure 2  Haematoxylin-eosin stain at 200×/0.45: some vesicular nuclei are observed among the small round blue cells characteristic of Merkel cell tumour.

Three stages have been described:
- Stage 1: clinical regional disease, tumour confined to the skin, absence of positive lymph nodes. T1A if smaller than 2 cm and T1B if greater.
- Stage 2: when there is regional lymph node involvement.
- Stage 3: metastatic disease.13

We are currently witnessing a rise in the incidence of this aggressive tumour, as described in the Anglo-Saxon literature consulted.10,11 There are no specific figures on the incidence in our environment. These same studies are making important advances in the pathogenesis of the tumour. In addition to the known influence of ultraviolet radiation, the role of specific molecular alterations that produce deletions and chromosomal rearrangements is being correlated. For the moment, it does not seem that one of these alterations could cause tumour development on its own. Most MCC cases are associated with more than 3 structural changes; deletion of the short arm of chromosome 1 (1p36), which appears in melanomas and neuroblastomas5,11; or loss of heterogeneity in chromosome 3p21, as observed in small cell lung cancer. Trisomies 1, 6, 11, and 183 also appear frequently. Current studies are focusing above all on the role of prior papillomavirus infection in the development of this tumour.3,11,12 All this research will make it possible to develop new therapeutic approaches in a relatively near future.

Treatment should be early and aggressive, and the Mohs technique should be used in small tumours, as was done in 2 of our patients. In Case 1, the patient delayed the consultation and the surgical decision for a long time. We believe that the tumour did not cause metastases due to the fact that cervical lymphadenectomy had taken place previously through laryngectomy. The sentinel node technique in this tumour does not ensure the existence of regional metastases and, in addition, sensitivity and specificity are lower than with the use of PET, although radiosensitivity varies according to the different histological types.13 Radiation therapy is recommended if the tumour resection has scarce safety margins or if there is lymph node invasion, existence of more than 10 mitoses per field, unresectable tumours or tumour involvement in vital areas.13 It is also justified in patients with relapses occurring in the same area, as in the second case presented. Use of the sentinel node technique in patients in stage 1 may discover the existence of occult
nodal invasion, since as many as 25% of patients present occult involvement at the time of diagnosis.

Combination chemotherapy has been used in cases of advanced disease with varying results. There are no clear results proving that its use extends disease-free time or improves survival. Cisplatin, doxorubicin, etoposide and bleomycin have all been used. Vincristine and CMF (cyclophosphamide, methotrexate, 5-fluorouracil) can also be associated.

Immunotherapy has also been used, with interferon alpha 2b, interferon gamma and melphalan (intratissional), as well as hyperthermia (HILP, hyperthermic isolated limb perfusion). The prognosis is poor, with local recurrence in the first year between 26% and 44% or even 75%-80% in head and neck tumours by incomplete tumour excision, with insufficient margins to avoid cosmetic defects in these areas. Survival is less than 55% at 3 years. Survival is directly proportional to aggressive treatment of the primary tumour and it is estimated to be 88% in the first year, 72% in the second and 55% in the third. Mortality is 45% for lesions in the head and neck and 29% for those located in limbs.

The following are considered to be poor prognostic factors: tumour larger than 2 cm in diameter, presence of metastasis at diagnosis, tumour located in the head and neck, small cell histological variety, more than 10 mitoses per high power field, early age of onset and male gender. The role of scintigraphy scans with gallium 131 or metaiodobenzylguanidine (MIBG) for the detection of recurrence is currently under discussion, as is the use of PET. PET was carried out only in the first patient to obtain greater certainty that there were no distant metastases, but its use is not mandatory.

Comprehensive monitoring is generally carried out through a periodic, monthly examination over the first 6 months, and every 2 or 3 months for the first 2 years, and then every 6–12 months for life.

**Conclusions**

Treatment of MCC requires early, correct diagnosis of the tumour, bearing in mind its clinical, histological and immunohistochemical characteristics. Surgery should be based on tumour stage at the time of diagnosis (2–3-cm margins, free of neoplasm through Mohs surgical technique) and, if possible, associated ipsilateral cervical lymph node dissection should also be carried out. Radiation therapy should be reserved for additional risk factors. Chemotherapy can be used in advanced and unresectable tumours or in inoperable patients. The monitoring of these tumours should be for life, due to their great capacity for locoregional recurrence.

**Conflict of Interests**

The authors have no conflicts of interest to declare.

**References**