Awareness for Merkel Cell Carcinoma: Consider it

ABSTRACT

We present a case of a 71-year-old Caucasian male complaining of left lateral lower eyelid swelling after an insect sting sensation. Physical examination showed an oval shaped lesion (half a centimetre diameter), mobile, with well-defined edges, soft consistency, and erythema. Palpation was painless and without lymph node involvement. The patient had a history of metastatic prostate adenocarcinoma. One week later, the lesion showed rapid growth (two centimetres diameter) with central ulceration. Incisional biopsy was made. Immunohistochemistry findings were suggestive of a primary neuroendocrine carcinoma: Merkel Cell Carcinoma. The patient underwent surgery with wide local excision, regional lymphadenectomy, and eyelid reconstruction.

Awareness of this type of tumor is crucial. A delay in diagnosis affects the prognosis of the disease significantly.

Keywords: Merkel Cell Carcinoma, Eyelid Neoplasms, Merkel Cells, Ophthalmology, Skin Neoplasms.

BACKGROUND

The significance of this case is related to the invasive potential of Merkel Cell Carcinoma. Its rarity may lead to a delay in the diagnosis. It must be considered in the differential diagnosis of eyelid neoplasms. Clinical suspicion is the key to earlier identification and to avoid a worse prognosis.

CASE PRESENTATION

We present a case of a 71-year-old Caucasian male complaining of left lateral lower eyelid swelling when attending the ophthalmology emergency. According to the patient, symptoms started after an insect sting sensation in the previous week, while driving. He was already medicated with oral bilastine and clarithromycin and topical fusidic acid and chloramphenicol ointments with no improvement.

The patient suffered a central retinal artery occlusion of the right eye in 1985.

In 2007, the patient was diagnosed with prostate adenocarcinoma and underwent radical perineal prostatectomy (pT3pN0). He was also submitted to radiation therapy after the surgery.

In 2012, the patient developed metastatic prostate adenocarcinoma (costal arch, dorsal vertebrae, spinal cord, femur, mandible, maxilla).

Since the diagnosis of prostate adenocarcinoma, the patient had been submitted to several treatments (bicalutamide, docetaxel, goserelin). He was currently medicated with abiraterone.

Physical examination showed an oval shaped protuberance (half a centimetre diameter), mobile, with well-defined edges, soft consistency, and erythema. Palpation was painless and without lymph node involvement.

Visual acuities were light perception in the right eye and 20/20 (Snellen Chart) in the left eye. Eye movements and slit-lamp biomicroscopy were normal. There was no abnormality of the right eyelids.

Ultrasound was not available in the emergency room, so computerized orbital tomography was performed. It showed nonspecific cutaneous and subcutaneous thickening of the lateral portion of the left inferior eyelid. (Figure 1). The
patient was medicated with local prednisolone and chloramphenicol ointment.

In the follow-up appointment (seven days after the emergency visit), the lesion was erythematous (with superficial telangiectasia), nodular and exophytic, significantly bigger (two centimetres diameter), mechanically inducing an ectropion of the lower eyelid with a central ulceration. Although the lesion itself lacked tenderness, the mechanical traction exerted was significant, and the patient started complaining of pain.

The lesion was rapidly growing, so we decided to better characterize it with an Orbital magnetic resonance imaging and an incisional biopsy. (Figure 2)

Orbital magnetic resonance imaging was performed (ten days after the emergency visit) to evaluate eyelid structures involvement. It showed an oval shaped solid lesion, limited to the eyelid, with no orbital invasion. However, all eyelid structures were involved. By this time, the lesion measured: craniocaudal - 2,1 centimetres; anteroposterior - 1,6 centimetres; transverse oblique - 2,5 centimetres. (Figure 3)

Histomorphological findings showed densely blue tumor cells located in the dermis. These cells were small and round with oval nuclei, had a “salt-and-pepper” chromatin pattern and a scant cytoplasm. Mitotic figures and apoptotic bodies were also present (Figure 4 A).

Immunohistochemistry findings were suggestive of a primary neuroendocrine tumor – Merkel Cell Carcinoma: CK8/18+ dot (Figure 4 B), CK20+ (Figure 4 C), synaptophysin+ (Figure 4 D), chromogranin + (Figure 4 E), CD56+ (Figure 4 F), BCL2+ (Figure 4 G), Ki67-95% (Figure 4 H), CD20-, CD10-, S100-, TTF1-.

**Differential diagnosis**

The differential diagnosis of eyelid neoplasms includes both benign and malignant lesions. Initial suspicion was inflammatory lesion associated with insect bite. Chalazion and Hordeolum were also considered due to common incidence. Rapid growth and changing characteristics were the keys to consider specific malignant eyelid tumors. Sebaceous cell carcinoma involves Zeis glands and alters the palpebral conjunctiva. Lymphoma, Merkel Cell Carcinoma and cutaneous metastatic prostate adenocarcinoma, remained as more plausible diagnosis. However, amelanocytic nodular melanoma, basal cell carcinoma and squamous cell carcinoma must always be considered due to their incidence. Cutaneous metastatic prostate adenocarcinoma is also a rare entity. Lesions have a papulonodular appearance, tend to be closer to the primary malignancy (abdominal skin) and multiple, but growth happens in several months, not weeks.

Histomorphology and immunohistochemistry are needed for final diagnosis.

Histomorphological findings were suggestive of Merkel Cell Carcinoma. Cutaneous metastatic prostate adenocarcinoma was excluded since it usually has a pattern of infiltrative disease with ill-formed glands.

However, other entities that comprise round blue cell tumors needed to be excluded through
immunohistochemistry: malignant lymphoma, metastatic lung small cell carcinoma, and amelanocytic nodular melanoma.

Merkel Cell Carcinoma possesses both neuroendocrine and epithelial features. It shows positivity for low-molecular-weight keratin (CK20).

Amelanocytic nodular melanoma should be positive for S100. Merkel Cell Carcinoma is negative for S100 and other melanoma markers.

Metastatic lung small cell carcinoma should be negative for CK20 and positive for TTF-1.

Malignant lymphoma lacks expression for epithelial markers (CK20) and neuroendocrine markers (synaptophysin and chromogranin) and usually expresses CD10 and CD20 (although CD10 can also be present in Merkel Cell Carcinoma). Additionally, metastatic prostate adenocarcinoma is generally negative for CK20.

**Treatment**

The patient underwent surgery with wide local excision, regional lymphadenectomy and eyelid reconstruction (median forehead flap). Margins were free, and there was no lymph node involvement. Since there was a pre-existing diminished visual acuity of the contralateral eye, adjuvant radiation therapy was not considered in this phase because of the risk of radiation retinopathy with loss of visual function.

**Outcome and follow-up**

The patient was classified, according to criteria of the American Joint Committee on Cancer, as pT2pN0M0 (TNM for Merkel Cell Carcinoma).

Positron emission tomography performed 5 months after surgery exhibited no disease activity related to Merkel Cell Carcinoma.

After 6 months of follow-up, the patient shows no sign of recurrence. The cosmetic result is always challenging due to the disturbance of the normal eyelid anatomy and mechanics. (Figure 5)

Long-term follow-up is necessary.

**DISCUSSION**

Merkel cell carcinoma is a rare form of malignant neoplasm with rapidly local dissemination and early lymph node metastasis. It is a neuroendocrine carcinoma in the dermo-epidermal junction that arises from Merkel Cells.

The function of these cells is not completely understood.

It occurs more frequently in older and immunosuppressed patients. The affected skin areas tend to be those exposed to the sun (ultraviolet radiation). Half of all Merkel Cell Carcinomas are located in the head and neck region, 5-10% occur in the eyelids (normally the upper eyelid). In addition, Merkel cell polyomavirus DNA appears to be present in 80% of Merkel Cell Carcinomas.
Initial clinical appearance may resemble more common diagnoses, as chalazion, hordeolum and basal cell carcinoma. Awareness of this type of tumor is crucial.7,8

Even in cases detected early, 20-60% already present lymphatic involvement.7

Lymph node involvement is correlated with increasing diameter of the lesion, but even small tumors are associated with regional nodal and distant metastatic disease.9,10

Metastases generally develop in the brain, skin, bone, lung, and liver.5

After the initial diagnosis, recurrences tend to occur within the first 24 months, and most of the patients present distant metastasis as the first recurrence event.4

Given the tendency of Merkel Cell Carcinoma to recur locally, wide local excision has been practiced as the standard of care.11

Current orientations of the National Comprehensive Cancer Network 2010 state that, in the management of patients with Merkel cell carcinoma who do not exhibit radiological or clinical evidence of ganglion involvement, a ganglion biopsy should be performed regardless of tumor size.12,13

Merkel cell carcinoma is radiosensitive, and adjuvant loco-regional radiotherapy (at a dose of 50–60 Gy) of the primary tumor region and the cervical lymph nodes is recommended. It minimizes local recurrence and improves survival.12

Adjuvant chemotherapy is associated with an increase in morbidity, and there is a lack of evidence concerning its role in improving survival or reducing the rates of recurrence. So it is not recommended in the majority of cases.12,14

The prognosis of Merkel Cell Carcinoma of the eyelid is generally poor.7

Follow-up is recommended with examination of local disease site, regional nodes and if indicated with imaging. There is increasing evidence that positron emission tomography combined with computer tomography could be a useful method for staging Merkel Cell Carcinoma.15

**LEARNING POINTS/TAKE HOME MESSAGES**

Merkel Cell Carcinoma is rare but aggressive;

Rapid local dissemination and lesion growth are the keys to early diagnosis;

Lymph node involvement is frequently present; therefore, sentinel lymph node biopsy should be performed;

Time sensitive prognosis;

Surgery should be done in a center with experience of eyelid reconstruction (Oculoplastic).

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**References**