A Rare Case of a Lower Lip Merkel Cell Carcinoma
Diagnosis and treatment

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Merkel cell carcinoma is (MCC) a rare type of skin malignancy that appears as a result of a disorganized multiplication of the Merkel cells and has a high rate of recurrence and metastases even from early stages. We describe the case of an 84-year old women diagnosed with Merkel cell carcinoma of the lower lip. Surgical treatment was realised with tumor excision and reconstruction using advancement flaps. Postoperative cosmetic and functional results were excellent, but invasion of the lateral margins, the patient's decision of refusing re-excision and delayed radiotherapy lead to a rapid recurrence within 3 weeks. Responsiveness to subsequent radiotherapy was very good with regression of the recurrent tumor and decreasing of the local discomfort. Surgical treatment Merkel cell carcinoma of the lip is sometimes very challenging for a surgeon due to the necessity of wide resection and of the patient's cosmetic concern. Radiotherapy remained an efficient therapy of Merkel cell carcinoma and should be used as a single or adjuvant therapy in situations where surgery cannot be applied, cisplatin chemotherapy being used for metastasis.

Keywords: Merkel cell carcinoma, immunohistochemistry, radiotherapy, Cisplatin

Merkel cell carcinoma (MCC) is a rare and extremely aggressive neuroendocrine skin tumor that usually affects white men over 70 years old, having anannual incidence of 0.6 per 100000 persons [1,2].

The etiology is unknown, but a few risk factors have been incriminated as age or immunocompromised status (organ transplantation, HIV infection) and long term ultraviolet light exposure [3]. Lately, Merkel cell carcinoma tumour genesis is associated in up to 80% of the cases with the oncogenic effect of a human polyomavirus (MCPyV) which is clonally incorporated [2].

The most common sites of presentation are head and neck in almost half of the cases, upper limbs (19%), lower limbs (16%) and trunk (11%) [4].

MCC of the lip is considered the most aggressive lip tumor [5], having a higher rate of invasion into bone and muscle, and the worst survival rate in comparison with other head and neck MCC [6].

This skin malignancy is associated with a mortality rate between 33% and 46%, which is higher than that described in patients with melanoma [2]. The mortality rate is highly associated with the stage of the disease, being influenced by nodal and distant metastasis. The 5 year survival rate in nodal-negative disease is almost 83%, in contrast with the nodal lesions that reduce the survival to 58% [2].

The main treatment of the local disease remained surgery, being associated with radiotherapy and in advanced cases with chemotherapy. Regular follow-up is important due to high risk of recurrence and high incidence of regional and distant metastasis [2].

We describe the case of an old female patient with a MCC of the lower lip discussing the clinical and pathological characteristics associated with diagnosis and possibilities of treatment.

Experimental part

An 84 year old woman, fair skin type, was referred by the dermatologist to our plastic surgery department with an elevated tumor mass situated on the lower lip. The tumor appeared 2 months before and increased in size, being also associated with a slightly discomfort. The patient was nonsmoker, had no medical history andworked in a steel coil factoryfor 25 years. Local examination showed a raised and diffuse 1.8/1.5 cm nodule with infiltrated and erythematous adjacent tegument (fig. 1). Dermoscopic evaluation revealed milky red and white structureless areas (fig. 2).

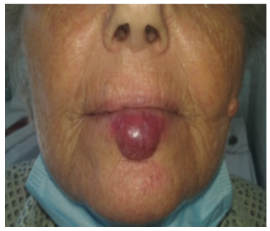

Fig. 1. Clinical aspect of lower lip tumor

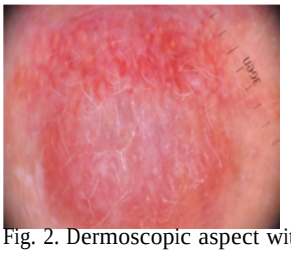

Fig. 2. Dermoscopic aspect with revealed milky red and white structureless areas

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Because of the clinical and dermoscopic aspect of the lesion, high suggestive for a malign tumor, we considered necessary to perform a biopsy. The clinical evaluation of regional adenopathy was negative and the general clinical examination found a normal weight patient, in a good general condition, without any particular findings. Before biopsy a local ethical agreement and informed consent of the patient were obtained. Also, a complete blood test evaluation was done. Laboratory tests revealed a moderate thrombocytopenia (100000platelets/μL) with a slightly decreased number of lymphocytes.

Histopathological examination of the tissue fragment, following incisional biopsy was suggestive for a MCC. In order to evaluate the extension of the tumor a computed tomography was performed. This examination showed a tumoral mass with muscle infiltration, presence of slightly enlarged submandibular lymph nodes, but no distant metastasis. Cervical lymph node ultrasound described the presence of bilateral cervical lymph nodes with a non-specific aspect. In the left submandibular zone a lymph node of 0.85/0.69 cm was present with increased vascularization and loss of corticomedullary differentiation.

Considering the size and the tumor'saggressivity surgical treatment of the tumor together with suspicious lymph node was performed under general anaesthesia.Because of the esthetical result the patient refused a surgery that would require a large defect and a difficult reconstruction with scars on the cheek. Excision of the tumor was realized with a 1.5 cm margin that permitted us to reconstruct the lower lip using advancement lip flaps (fig. 3). Dissection and excision of the suspicious lymph node was also realized. Postoperative functional and cosmetic results were favourable.

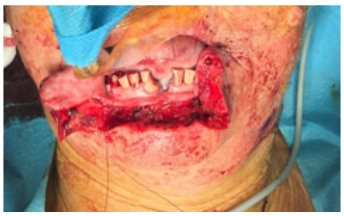

Fig. 3. Merkel cell carcinoma excision with a 1.5 cm margin

Histopathological examination revealed an irregular contour tumor, measuring 1.8/1.7/1.6 cm with dermal aggregation of tumor cells characterized by scanty cytoplasm and basophilic nuclei with high mitotic activity (> 80 mitosis/mm^2),that is the most common feature for intermediate subtype of MCC (fig. 4). No presence of lymphovascular invasion or tumor-infiltrating lymphocytes was found. The tumor had a thickness of 16 mm and a nodular growth pattern. Unfortunately, the lateral margins status was confirmed as positive.

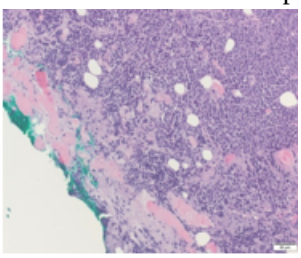

Fig. 4. Tumoral cells infiltrating adipose and muscle tissue (HE; x20)

Immunohistochemistry indicated that tumor cells expressed both epithelial (cytokeratin-CK 20, pankeratin) and neuroendocrine (chromogranin A) markers, characteristic for MCC (fig. 5). CK20 has a specific paranuclear dot-like staining (fig. 6). Staining for Vimentin, S100, Melan A and CD 45 was negative.The submandibular lymph node was free of tumor cells. According to TNM stabilization our patient had MCC stage I (T1N0M0).

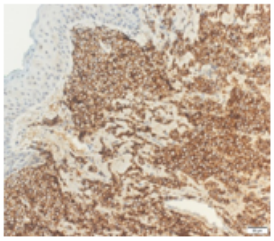

Fig. 5. Chromogranin A diffusely positive in tumoral cells (Chromogranin A; x20)

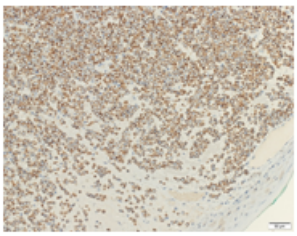

Fig. 6. CK 20 diffusely positive in tumoral cells, with annular pattern

Considering the positive lateral margins, another re-excision was proposed. The patient refused it and was referred to the oncologist who recommended radiotherapy that was scheduled in two months. After 3 weeks from the surgery the patient started to fell discomfort and a small nodule started to appear on the left side of the scar. The nodule started to grow and in 6 weeks became more and more painful, being a local recurrence of the primary tumor (fig. 7). The patient started radiotherapy and after 20 cures the tumor regressed and disappeared (fig.8).

Three months follow-up showed a thin scar with no local recurrence, no local discomfort and with good functional results.

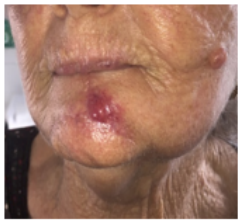

Fig. 7. Local recurrence of the primary tumor

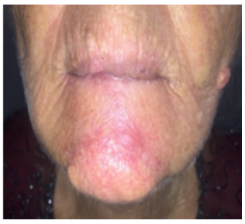

Fig. 8. Local recurrence regression after radiotherapy (9 weeks follow up)

Results and discussions

We reported the case of a female patient diagnosed with MCC of the lower lipsstage I with rapid recurrence of tumor after primary surgery. Even though, the small size of the tumor (< 2 cm) without node or distant metastasis, permitted to be included in an incipient stage, this form of MCC might have a poor prognosis due to its location, patient age, positive margins and histopathological characteristics (high mitotic rate, nodular growth pattern).

Merkel cells were described for the first time by Friedrich Merkel in 1875 as *Tastzellen* (touch cells) due to their interconnection with nerve fibres. These are located in the basal layer of the epidermis and can have a role of mechanoreceptor when are in contact to nerveterminals and a role of neuroendocrine cells when are located in the skin being characterized by neuroendocrine granule (neuron-specific enolase) and keratin filament (cytokeratin-20) [7].

The etiology is considered to be multifactorial: increased age, immunocompromised status, ultraviolet exposed fair skin and viral factor (Merkel cell polyomavirus) might be involved in MCC development. Despite of the fact that the Merkel cell polyomavirus is associated with

the majority of MCC, until now, the connection between viral status and clinical evolution is not certain [8]. In our case, the patient had an immunocompetent status without UV exposure. Although she worked in a steel coil factory, we could not asses if constant exposure to different chemical substances could have been a risk factor. Unfortunately, we were unable to determinate the presence of Merkel cell polyomavirus. The clinical examination of the tumor describes it as solid, red-violet, rapidly-growing cutaneous lesion with a dome-shape that produces no pain [9]. Usually the epidermis is intact and the clinical differential diagnosis includes squamous cell carcinoma, cysts, skin metastasis, and melanoma or malignant lymphoma [10]. In about 50% of the cases the tumor appears on the head and neck and up to 10% on the eyelid [11]. Dermoscopy might be a diagnostic tool although the differential diagnosis with amelanotic melanoma, basal cell carcinoma, pyogenic granuloma or skin metastasis is difficult to be realized. The dermoscopic aspect of MCC is influenced by the accelerated neoangeogenesis due to the specific fast growing tumor. The presence of numerous vessels and milky red areas associated with shiny white areas in the centre are the main characteristics of this tumor, which is often confused with amelanotic melanoma [12]. In our case, clinical aspect of rapid increasing red nodule with milky red and white structureless areas on dermoscopy examination was high sensitive for a malignant tumor, but very difficult to specify the type of the tumor.

Diagnosis is realized through an incisional or excisional biopsy. Fine needle aspirate can also be performed, but is difficult to differentiate MCC from other neoplasms. The best method to confirm a diagnosis is histo-pathological examination on haematoxylin- eosin slides associated with immunohistochemical analysis. Histological, MCC consists of densely round blue cells that contain neurosecretory type granules, being situated in the dermis and in some cases also in epidermis. These are arranged in nests or ribbons, being surrounded by lymphocytes, with numerous mitosis and frequent lymphovascular invasion. Immunohistochemistry is essential for realizing differential diagnosis. Perinuclear staining with cytokeratin 20 is the main diagnostic tool with the highest degree of specificity [13,14]. MCC is also stain positive to neuroendocrine markers as CD56, chromogranin and neurofilament. The histological examination reveals three subtypes: *trabecular*, the most differentiated and found in mixed tumors; *intermediate,* the most common with an excessive mitotic rate and *the small cells subtype,* undifferentiated, with the worst prognosis [15]. Our patient presented the intermediate type of MCC.

Some of the poor prognostic factors are considered male gender, vitamin D deficiency, advanced age (75 years), lip location, immunosuppressive status,tumor dimension and positive margins [16]. From the histological characteristics, lymphovascular invasion, mitosis number, growth pattern and lymph node number have a poor prognosis [17]. In our case the age, lip location, positive margins, numbers of mitosis and growth pattern were factors for a poor prognostic. Good prognosis has been associated with tumor size smaller than 2cm, female gender and local radiotherapy [18]. Patients with Merkel cell carcinoma are susceptible to secondary cancers, mostly malignant melanoma or hematologic diseases, which decrease the overall survival.

The staging of this type of skin malignancy is according to the dimension of the tumor, node and distant metastasis [8]. The case that we reported presented a tumor less than 2 cm without regional or distant metastasis which was classified as stage I. The current treatment relies on several features comprehending the stage at presentation, regional lymph node status and comorbidities. The primary treatment option for localized MCC is surgery. Wide large excision with 1 cm clinically free margin if the tumor has less than 2 cm in size and 2-3 cm free margin for those bigger than 2 cm is highly recommended [18]. Deep margins are also necessary through the muscle fascia or pericranium. The suggestion is to achieve histological confirmed margins of 1cm in healthy tissue [16]. Patients with positive margins should undergo re-excision due to the unfavourable prognosis and to the risk of recurrence [2]. We performed a wide excision with 1.5 cm safe margins according to the dimension of the tumor (less than 2 cm). Complete lymph node dissection is indicated when lymph nodes are clinically present and when sentinel lymph node is positive [2]. In general sentinel lymph node biopsy is recommended due to the significant rate of occult nodal metastasis [11], but according to the National Comprehensive Cancer Network sentinel lymph node biopsy for head and neck lesions is less useful due to complex lymphatic drainage and false negative results [19]. In this context, we decided not to perform a sentinel lymph node biopsy, but to excise the suspicious submandibular lymph node discovered in ultrasound.

Radiotherapy has an important role in the treatment of Merkel cell carcinoma because of the radiosensitivity of the tumor, either as adjuvant therapy after excision, lowering the rate of recurrences or as palliative treatment for inoperable lesions. This can lower the recurrence rate and improve overall survival [5]. The radiation therapy should include also the area of local vessels and first lymph nodes [17]. Because of positive margins after excision, our patient received the indication for radiotherapy with favorable results. In case of distant metastasis MCC had indication for chemotherapy. Even though MCC responds to chemotherapy; this is not a durable response, increasing overall morbidity. In general are used cisplastin or carboplantin, with etoposid and topotecan. Cisplatin is a chemotherapeutic agent that is also used in treating testicular and ovaries cancer and acts on inhibiting DNA replication carcinogenic cells (figure 9) [20,21]. The general survival is about 10 months due to the high recurrence after treatment and also because of the significant toxicity [22].

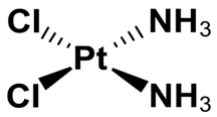

Fig. 9. Cisplatin formula

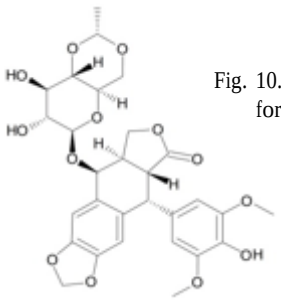

Fig. 10. Etoposid formula

Several studies are ongoing for studying the role of immunotherapy, autologous T cell therapy and hormone like drugs in treatment of MCC having incipient but effective results [23,24]. Being known that polyomavirus might be involved in this pathology, in the future this malignancy might be prevented and also treated with antiviral therapy [25]. Local recurrences usually occur in the first 6 to 12 months after diagnosis, a periodic follow up being recommended [26]. Distant metastases are observed in the first 3 years in the lungs, skin, brain, bones or liver [2]. Regular follow-up is very important in this period and should include anultrasound and a chest radiograph at 3 months

in the first 2 years and further at6 months [5]. A computed tomography of the head and neck is also recommended after 3 months from diagnosis [2].

MCC is a rare and aggressive tumor with a high rate of recurrence and metastasis. MCC of the lip is considered the most aggressive lip tumor. The management of lip MCC can present a special problem since achieving an adequate wide resection in these patients is often difficult and since the lymphatic drainage from the primary tumors in this region is highly variable. In these patients radiotherapy after surgery is in general recommended.

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