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# Merkel Cell Carcinoma: A Case Report and Literature Review

Motsatsa Mosolino G[1*], El Alouani C[1], Camilia D[2], Boussif M[3], Azzahiri I[3], Dref M[2], Diana A[3], Barkiche S[1], Oumghar N[1], Fakhri A[2], Benzalim M[3], Alj S[3], Darfaou, M[1], El Omrani A[1], Khouchani M[1]

[1]Radiation Oncology Department, Hospital of Oncology and Hematology, Mohammed VI University Hospital, Cadi Ayyad University, Marrakech, Morocco
[2]Anatomopathology Department, Ar-Razi Hospital, Mohammed VI University Hospital, Cadi Ayyad University, Marrakech, Morocco
[3]Radiology Department, Ibn Tofail Hospita, Mohammed VI University Hospital, Cadi Ayyad University, Marrakech, Morocco

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***Corresponding author:** Motsatsa Mosolino G
Radiation Oncology Department, Hospital of Oncology and Hematology, Mohammed VI University Hospital, Cadi Ayyad University, Marrakech, Morocco

**Abstract** **Case Report**

Merkel cell carcinoma (MCC) is a rare but very aggressive cutaneous malignant tumor of neuroendocrine origin with an increasing incidence rate. Its pathogenesis is linked to Merkel cell polyomavirus, and advanced age, white skin exposed to UV and immunodeficiency are among these risk factors. Its treatment is based on surgery in localized disease and immunotherapy in locally advanced or metastatic disease. We report here the case of a 79-year-old patient, followed at the Oncology-Radiotherapy Department of the Mohammed VI University Hospital in Marrakech, for treatment of a MCC of the lower lip. He benefited from primary surgery followed by adjuvant radiotherapy with an encouraging response. Currently he is under surveillance. Knowledge of this rare malignant tumor will allow health professionals to improve its management by establishing the diagnosis early and indicating adequate treatment, because therapeutic advances in recent years have significantly improved survival.

**Keywords**: Merkel cell carcinoma, surgery, immunotherapy, CD8 T lymphocyte, prognosis.



## INTRODUCTION

Merkel cell carcinoma (MCC) is a rare, potentially fatal malignant skin tumor of neuroendocrine origin. Global annual incidence rates of MCC are reported to be between 0.19 and 0.82 per 100,000 person-years and are increasing [1-5]. The pathogenesis of the disease is often linked to Merkel cell polyomavirus (MCPyV) [6-11]. Risk factors for MCC include older age [12, 13], white people with prolonged exposure to sunlight or UV rays [14], and immunodeficiency [14, 15]. Clinically, MCC often presents in the form of a nodule or rarely a plaque, asymptomatic, firm, rapidly growing [16], preferentially located in the head or neck [13, 17, 18]. The diagnosis is based on histopathological study and medical imaging.

Surgery remains the first therapeutic option in the treatment of MCC, with margins of 1 to 2 cm [19] associated or not with radiotherapy. Exclusive radiotherapy may be indicated in cases of unresectable disease or contraindication to surgery. Locally advanced or metastatic disease is treated with immunotherapy because chemotherapy provides transient responses.

Age over 60 years, male gender, head or neck location and stage of the disease at the time of diagnosis are factors influencing the prognosis of the disease [13, 14, 20, 21]. The overall 5-year survival rate is 40% [22].

We present here the case of a 79-year-old patient suffering from Merkel cell carcinoma followed in the Department of Oncology-Radiotherapy of the Mohammed VI University Hospital of Marrakech, with the aim of providing in-depth knowledge of MCC to nursing staff and to the general population because knowledge of this rare malignant tumor will allow these health professionals to establish an early diagnosis and initiate adequate treatment.

## CASE REPORT

At the beginning of July 2023, a 79-year-old patient, a former farmer, consulted the Maxillofacial Surgery, Aesthetics and Stomatology Department of the Mohammed VI University Hospital for treatment of an upper lip nodule that had been present for 5 months and had recently fistulized.

A skin biopsy was performed and on histopathological study, it was a morphological and immunohistochemical appearance of a Merkel cell carcinoma.

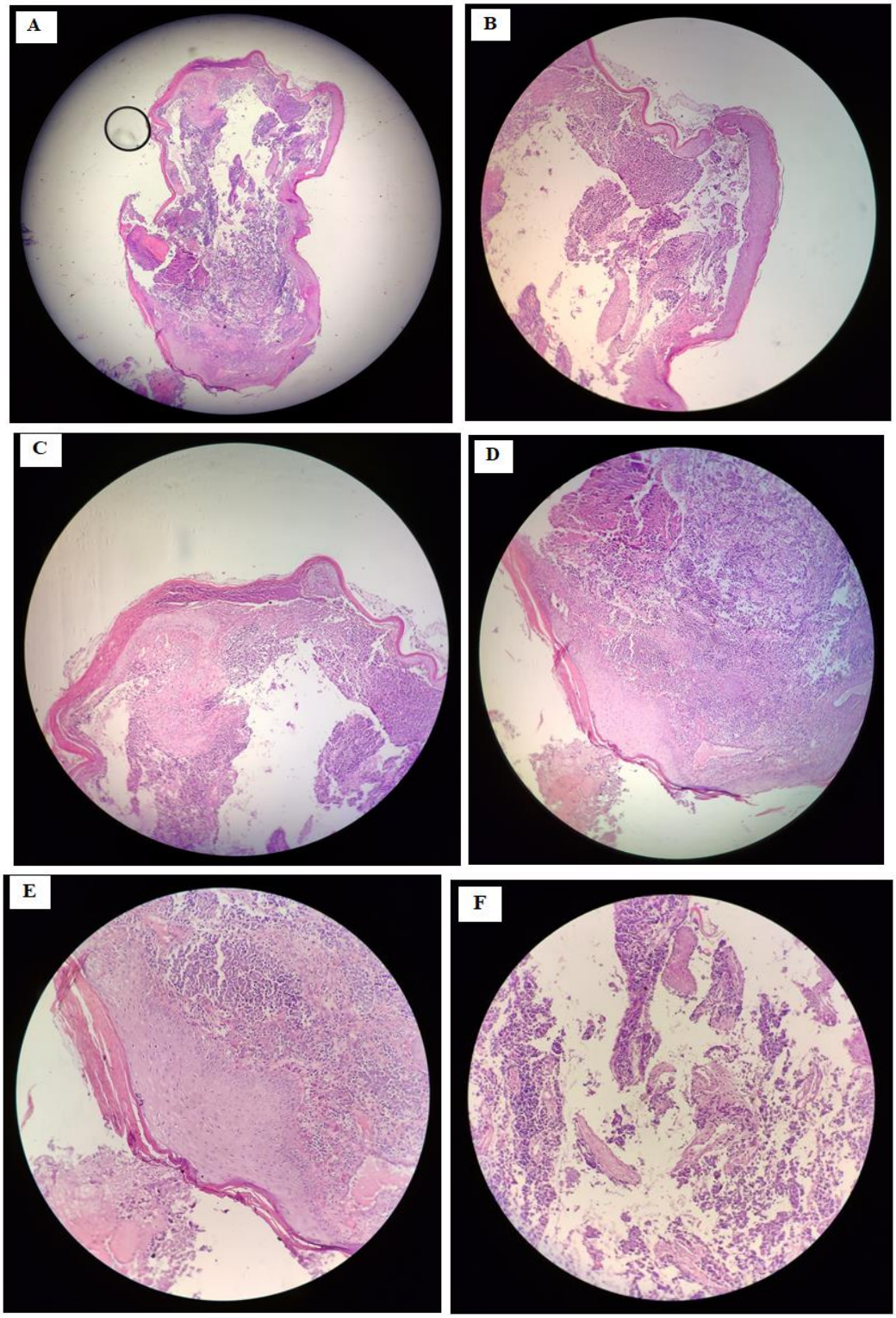


**Figure 1: Images A, B, C, D, E and F: Photomicrographs showing a Expansive, diffuse, infiltrative proliferation, arranged in lobules and clusters of endocrinoid architecture, made up of monomorphic cells compatible with Merkel Cell Carcinoma**

The cervico-facial CT in August 2023 revealed an ulcero-budding, exophytic upper labial lesion process , fairly well limited, with irregular contours, measuring 46.5x39x49 mm; posteriorly, it infiltrates the upper labial subcutaneous soft parts and comes into intimate contact with the right alveolar process of the maxillary

bone which appears condensed in places with rupture of the bone cortex opposite the 13th dental root; above, it is responsible for a nodular infiltration of the soft subcutaneous tissues of the right cheek and comes into contact with the ipsilateral nostril. Outwards and downwards, it infiltrates the right corner of the lip; medially, it infiltrates the upper labial region which appears thickened, measuring 13 mm in maximum thickness. It is associated with lymphadenopathies (n=3) under the chin (20x19 mm for the largest) and high right jugulocarotid (22x20 mm for the largest).

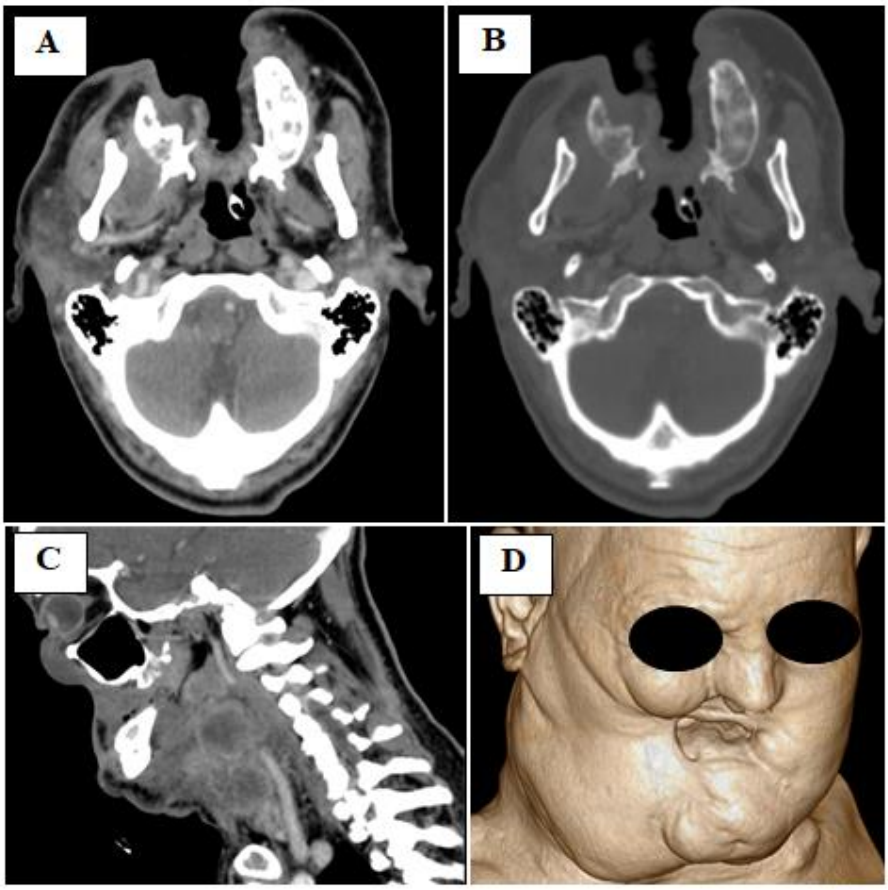


**Figure 2: Cervico-facial CT in August 2023: Axial section in parenchymal (A) and bony (B) window, showing the ulcerative-budding upper labial process, heterogeneously enhanced after injection of the PDC, with rupture of the bony cortex next to the 13th dental root. (C) Sagittal section with injection of contrast product, showing the upper labial process with magma of right jugulocarotid lymphadenopathy, encompassing the vascular axis which remains permeable. (D) 3D VRT reconstruction**

Then, the patient underwent primary surgery in November 2023: tumor excision coupled with bilateral lymph node dissection (right and left retro-spinal chains, right and left jugulocarotid, left posterior and anteromedial) and reconstruction by flap of the pectoralis major muscle.

The histopathological study of the surgical specimen confirmed the diagnosis of a MCC, the tumor measured 5.5x5x2.5 cm, ulcerated the epidermis on the surface and was largely necrotic with vascular emboli. The excision limits passed into healthy tissue; the closest, the deep limit, was 2.5 cm. Of 46 lymph nodes collected, 5 from the left posterior chain were metastatic.

Referred to our department for adjuvant treatment, upon admission in January 2024, he was a conscious patient, hemodynamically and respiratory stable. On physical examination, we observed an operating wound in the process of healing.

A CT-TAP from the same January 2024 revealed no secondary localization. Adjuvant radiotherapy was indicated at a dose of 60Gy. The evaluation CT-TAPs of April and July 2024 showed no abnormalities.

## DISCUSSION

MCC is a rare, potentially fatal, malignant skin tumor of neuroendocrine origin, first described by Toker in 1972 under the name trabecular carcinoma of the skin [23]. Its global annual incidence rates are between 0.19 and 0.82 per 100,000 person-years and are increasing,

this latter trend being justified by advances in diagnosis and the aging of the population [1-5].

The main cause of MCC, accounting for more than 80% of cases, is a mutated form of Merkel cell polyomavirus (MCPyV) [6-11]. Specific risk factors for MCC include: - advanced age, the average age at diagnosis is 75.5 years [12], more than 73 years [13]. An American study of 27,105 cases of MCC between 2001 and 2015 estimated that only 0.07% of cases were aged under 30 years [24]; - people with white skin and prolonged exposure to the sun or UV rays [14] are at greater risk of developing MCC; - immunodeficiency [14, 15]; - people with a history of chronic inflammatory disorders [25] and organ transplant recipients [26-28]. Our patient's risk factors included advanced age and chronic exposure to the sun (former farmer), and he had not benefited from MCPyV research.

MCC presents clinically in the form of a nodule or rarely a plaque, asymptomatic, firm, rapidly growing [16]. The most common locations of MCC are the head and neck in 42.7% [12] or more than 50% of cases [17, 18], followed by the extremities (lower and upper limbs) [29]. Which corroborates with our case who consulted after fistulization of a nodule of the lower lip (head).

The definitive diagnosis of MCC is made by a histopathological study after skin biopsy. Our patient benefited from this biopsy. In addition to a biopsy, lymph node evaluation (clinical, radiological or surgical) should be performed in all patients, regardless of stage, because the disease generally has a rapidly progressive course [30]. In our case, clinically, the patient presented with cervical lymphadenopathy, confirmed by imaging (CT) and the histopathological study of lymph node dissection revealed metastatic lymph nodes.

On histopathological study, MCC reveals itself as a dermal proliferation of small blue cells in sheets or in a trabecular network. The cells contain little cytoplasm and round nuclei containing finely granular chromatin and discrete nucleoli. Numerous mitotic figures are usually visible, and the tumor may exhibit vascular invasion, perineural invasion, or cellular necrosis. On immunohistochemistry, cells are positive for cytokeratin-20, considered highly sensitive, neuron-specific enolase, epithelial membrane antigen, CAM 5.2, and neuroendocrine markers such as synaptophysin and chromogranin. Importantly, the cells are negative for TTF-1, S-100, and leukocyte common antigen [16].

Medical imaging provides important information in therapeutic planning, especially surgical planning. In a prospective study conducted in Australia, 18-FDG PET/CT was shown to have high sensitivity and specificity in staging MCC. Pre-treatment staging influenced the treatment decision by allowing disease worsening in 25.9% of patients with MCC [31]. 18-FDG PET/CT has also been used to monitor the response of metastatic MCC to immunotherapy [32].

Surgery remains the first therapeutic option in the treatment of MCC, with margins of 1 to 2 cm [19] associated or not with lymph node dissection. A wide excision associated with lymph node dissection was indicated in our patient. Mohs micrographic surgery is also performed and has been shown to be non-inferior to wide local excision in several studies [33-35].

Adjuvant radiotherapy is also indicated (50-66 Gy and >10 Gy on tumor bed) [14, 36, 37]. Sanne E. Uitentuis *et al*., [12] suggested that surgery combined with radiotherapy may be more valuable than surgery alone. This conclusion is consistent with those of other studies which showed higher survival in patients treated with surgery combined with adjuvant radiotherapy [1-4]. When the tumor is unresectable or surgery is contraindicated, definitive radiotherapy may be indicated as an alternative to surgery at doses of 60-66Gy [37], 5-year OS rates of 40% have been reported with this technique [38].

Standard surgery improves median survival and long-term survival compared to radiotherapy alone in patients with resectable MCC. In a retrospective American study conducted on 2454 patients with MCC in the United States who received either surgery or radiotherapy as primary treatment, stage I and II patients who received surgery presented a median OS of 76 months (compared to 25 months in those receiving radiotherapy). In stage III patients, the median OS was 30 and 15 months in the surgery and radiotherapy groups, respectively [39].

In recent years, immunotherapy has emerged as an effective therapy for MCC. First, MCC is considered an immunogenic cancer due to the association between immunosuppression and disease prognosis. Second, patients with high CD8 T cell infiltration in MCC had better outcomes compared to those with lower infiltration (100 vs. 60% MCC specific survival), thus suggesting the potential role of CD8 T cells in MCC tumor environment [40]. Third, the presence of MCPyV-specific CD8 T cells and MCC-infiltrating lymphocytes was subsequently correlated with PDL-1 expression [41]. These findings suggest that increased immune function would promote positive outcomes of MCC and that therapies targeting PD (L)-1 would be effective in treating the disease.

In the CheckMate 358 Virus-Associated Cancer Types study, patients with resectable MCC received neoadjuvant nivolumab on days 1 and 15, surgery on day 29. 39 patients with resectable MCC AJCC stage IIA-IV patients received nivolumab. Three patients (7.7%) did not undergo surgery due to tumor progression (n=1) or adverse events (n=2). Among the 36 patients who underwent surgery, 17 (47.2%) achieved a pathologic

complete response. No patient with pCR had tumor relapse during observation [42]. This study validated neoadjuvant nivolumab in resectable or unresectable disease. Neoadjuvant immunotherapy, administered preoperatively with a macroscopic tumor in place, has the potential to induce long-lasting systemic antitumor immunity to prevent postoperative relapse [43].

In locally advanced or metastatic disease, chemotherapy, most often a combination of cisplatin and etoposide or based on anthracyclines, is recommended but its responses are transient. Nghiem *et al*., [44] report objective response rates (ORR) of 20 to 61% after chemotherapy, with better results in first line compared to second line, and a response duration of 8 months or less.

Avelumab, an anti-PDL1 human IgG1 monoclonal antibody, was approved for second-line use in metastatic MCC in the United States [45], Europe [46], Australia [47] after the results of a JAVELIN Merkel 200 clinical trial, in which 88 adult patients with metastatic MCC previously treated with chemotherapy received avelumab intravenously. After at least 1 year of follow-up, the ORRs were 33.0%, with 11.4 and 21.6% of patients achieving complete and partial responses, respectively. Median overall survival was 12.9 months, far exceeding historical OS results achieved with other second-line treatments [48, 49].

The SPEAR-Merkel study [50] evaluated treatment patterns in 94 patients with locally advanced or metastatic MCC. 28 received avelumab, 26 non-avelumab immunotherapy, and 40 chemotherapy. The overall response rate was 64.3%, 61.5% and 42.5%, respectively, with median survival rates of 11.4, 8.1 and 6.1 months, and the median OS was not reached. This study showed that patients with locally advanced or metastatic MCC treated with immunotherapy, especially avelumab, had better outcomes compared to chemotherapy in clinical practice.

Shailender Bhatia S *et al*., [51] examined clinical outcomes in patients with advanced MCC (stage IIIB/IV) treated with avelumab at US academic medical centers between 2017 and 2019. 90 patients with advanced MCC (82%, stage IV; 18%, stage IIIB) received avelumab. Median follow-up was 20.8 months (95% CI: 19.1 to 24.2). 73 patients (81%) received avelumab as first-line treatment for advanced MCC, while 17 (19%) received avelumab as second-line treatment or later. Patients had a median PFS and OS of 24.4 and 30.7 months, respectively. This study demonstrated that patients with advanced MCC had positive responses to avelumab.

Pembrolizumab, a humanized IgG4 antiPD1 monoclonal antibody, has also been evaluated [52]. In the Cancer Immunotherapy Trials Network-09/Keynote 017 trial [53], 50 patients with locally advanced MCC received pembrolizumab for up to 2 years. The objective response rate (ORR) to pembrolizumab was 56% (complete response [24%] plus partial response [32%]; 95% CI, 41.3% to 70.0%), with ORRs of 59%. % for viral positive tumors and 53% for viral negative tumors. Median follow-up duration was 14.9 months (range, 0.4 to 36.4+ months). The 24-month PFS rate was 48.3% and the median PFS duration was 16.8 months (95% CI, 4.6 months to not estimable). The 24-month OS rate was 68.7% and the median OS duration was not reached. Current recommendations from the National Comprehensive Cancer Network include the use of pembrolizumab as a systemic treatment option in patients with locally advanced and metastatic MCC [15, 37].

Age over 60 years, male gender, head or neck location, stage of the disease at the time of diagnosis are prognostic factors for the disease [13, 14, 20, 21]. In a Dutch study of 1977 patients with MCC, diagnosed between 1993 and 2016, the 5-year relative survival was low (63.0%). Mortality was higher in men (hazard ratio [HR], 1.24; 95% confidence interval [CI], 1.11-1.39), in older men (HR, 1.07; CI at 95%: 1.06-1.07) and with lymph node extension of the disease (HR, 1.26; 95% CI: 1.08-1.48) and with distant extension of the disease (HR, 2.44; 95% CI, 1.99-2.99) [12]. Mary Brady *et al.*, [16] estimated five-year overall survival of 51%, 35%, and 14% for local, nodal, and distant disease, respectively. Sentinel lymph node biopsy negativity is a strong predictor of longer disease-free survival and overall survival. Additionally, patients with tumors less than 2 cm have a higher ten-year survival than those with tumors larger than 2 cm. Immunosuppression is also associated with decreased survival in patients with MCC [54].

Patients with MCC should be followed every three to six months for the first three years and every six to 12 months thereafter. This monitoring must include a complete clinical examination (of the skin, lymph node areas and areas of possible metastases) and medical imaging (CT). Our patient is currently under surveillance.

## CONCLUSION

This work reports a case of Merkel cell carcinoma, a rare malignant tumor with an often poor prognosis, in a 79-year-old patient who responded well to treatment and who is currently under surveillance.

Despite its prognosis, MCC has benefited, in recent years, from several diagnostic and therapeutic advances, especially with immunotherapy.

Its rapid spread pushes us to diagnose it a little earlier because local disease resected with negative margins has better recurrence-free survival and better overall survival than other forms of the disease. This

early diagnosis would save us from mutilating surgery, recurrences or progression.

In-depth knowledge of this rare tumor will allow healthcare personnel to improve its treatment. This was the objective of this case presentation.

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