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Case and Review

Merkel Cell Carcinoma of the Head in a Young African Albino Woman with HIV/HTLV-1 Coinfection Associated with Multiple Squamous Cell Carcinomas

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Keywords
Merkel cell carcinoma · HIV · HTLV-1 · Ocular-cutaneous albinism · Squamous cell carcinoma · Africa

Abstract
Merkel cell carcinoma (MCC) is a rare cutaneous neoplasm of presumed neuroendocrine origin, with aggressive behavior and poor prognosis, that tends to have an increased incidence among elderly Caucasians and immunosuppressed individuals. MCC is either associated with a clonal integration of the Merkel cell polyoma virus into the host genome or with genomic alterations caused by chronic UV exposure. Tumors of either carcinogenesis show epithelial, neuroendocrine, and B-lymphoid lineage markers. HIV-infected African albinos have a higher risk of developing skin cancers, including MCC, in comparison with the general population. We report a case of MCC of the head in a young albino woman with a HIV/HTLV-1 coinfection.

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The patient also suffered from multiple squamous cell carcinomas of the scalp, face, lip, and ears, suggesting an UV carcinogenesis of MCC. The purpose of this case report is to emphasize the relationship between immunosuppression (HIV/HTLV-1 coinfection, chronic sun exposure, ocular-cutaneous albinism, pregnancy) and MCC. It highlights the importance of early diagnosis, dermatological screening with a risk-stratified surveillance, particularly in immunosuppressed albino patients in sub-Saharan Africa, and multidisciplinary management of this biologically unique cutaneous cancer.

Introduction

Merkel cell carcinoma (MCC) is a rare cutaneous tumor of disputable origin associated with advanced age, fair skin phenotype, and immunosuppression. Two forms of MCC carcinogenesis have been described: tumors are either associated with Merkel cell polyomavirus (MCPyV) or with genetic alterations characteristic for chronic UV exposure. In either case, it is a highly immunogenic tumor caused by constitutive expression of viral proteins in MCPyV-positive MCCs and very high frequency of DNA mutations in UV-associated MCCs [1–3]. The tumor is characterized by trilinear differentiation, comprising the expression of neuroendocrine, epithelial, and lymphoid lineage markers [2–4]. The incidence rate of MCC is variable across different geographical regions of the world with alarming changing incidence trends with aging in both sexes [2, 3, 5]. MCC is regarded as a lethal tumor, with a mortality exceeding that of melanoma based on case fatality rates, with a 5-year disease-specific survival estimated at between 33 and 64% [3, 6]. Almost one-third of the patients present at primary diagnosis with locoregional or in transit metastases [3]. In both sexes, the most frequent localization of the tumor at diagnosis is the head and neck regions accounting for half of the cases, followed by localization on the proximal limbs, lower limbs, and trunk [6, 7]. Frequently, MCC develops as a rapidly expanding, purplish nodule. The acronym AEIOU (standing for asymptomatic, expanding rapidly, immunosuppressed, old age, and UV-exposed) has been used to recall relevant clinical features of MCC [8].

Common risk factors of developing MCC include fair skin, cumulative solar exposure, and dysregulation of the immune system. A history of skin cancer (basal cell carcinoma [BCC], squamous cell carcinoma [SCC], or melanoma) is also linked with a greater risk for MCC [3, 7]. Consequently, genetic conditions prone to develop skin cancers (ocular-cutaneous albinism [OCA], xeroderma pigmentosum) have an increased risk for MCC. MCC is known to arise more frequently and behave more aggressively in immunocompromised individuals including those with HIV infection, solid organ transplant recipients, autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus), and as a second tumor in patients with hematologic malignancies suggesting that the immune function plays a critical role in the outcome of MCC [1, 2]. Lacking photo protection provided by melanin synthesis, albinos are highly susceptible to UV-induced skin cancers. MCC is particularly uncommon in African albinos. We report a case of MCC of the head in a young African albino woman with HIV/HTLV-1 coinfection, associated with multiple SCCs of the scalp, face, lip, and ears.

Case Report

A 27-year-old albino woman of sub-Saharan African ancestry was referred from a regional hospital for assessment and treatment of a nodular lesion of the scalp which had

emerged 8 months earlier and enlarged rapidly. Her medical history was notable for HIV infection, a BCC of the neck removed elsewhere, and significant sun exposure. Her family medical history was noncontributory. Physical examination revealed a large, purplish, protruding tumor (6.5/3.5 cm in size) on the left temporoparietal aspect of the head. The tumor was tender, ulcerative and showed signs of secondary bacterial infection (Fig. 1a). She presented marked solar damage illustrated by solar elastosis, multiple actinic keratoses, a patch of Bowen's disease on the neck, and several erosive and hyperkeratotic skin lesions on sun-exposed areas, which were clinically suggestive of non-melanoma skin cancers. Apart from these findings, a review of the systems was unremarkable. We considered in differential diagnosis: cutaneous lymphoma, malignant melanoma, MCC, and SCC. The baseline blood investigations revealed mild anemia (Hb 9.1 g/dL; RBC 3.32×10^{12}), hypoalbuminemia (29 g/dL), and a deranged lymphocytic subset analysis (low $CD4^+$ cell count of 10^9 cells/μL and high $CD8^+$cell count of 1,849 cells/μL). Viral studies confirmed HIV seropositivity (viral load of 640 RNA copies/mL), past exposure to EBV, reactivation of CMV (both IgM and IgG positive), hepatitis B immunity as a result of past exposure, and HTLV-1 antibody screen positivity. The culture of the pus swab demonstrated *Enterobacter cloacae* and *Enterococcus faecalis* growth. Several skin biopsies were obtained from the scalp tumor and from suspected SCCs/BCCs of the neck, eyebrow, upper lip, and ears.

Histological examination of the scalp tumor showed an exophytic, ulcerated nodule consisting of extensively invaded dermis by a poorly differentiated tumor (Fig. 2a). The neoplastic cells were arranged in vague nests and sheets showing high mitotic activity and a degree of molding. The tumor was widely infiltrating up to subcutaneous tissue and focally in the skeletal muscles with evidence of both perineural and lymphovascular invasion. Furthermore, a multicentric, moderately differentiated, keratinized SCC was seen adjacent to the tumor (Fig. 2b). Immunoperoxidase stains revealed paranuclear dot-like positivity for cytokeratin CK20 (Fig. 2c), extensive positivity for neuroendocrine markers: synaptophysin and neuron-specific enolase, and for CD56 (Fig. 2d, e, f). More focal positivity was demonstrated for chromogranin A stain. The electron microscopy illustrated neurosecretory granules within the cytoplasm (Fig. 2g) confirming the diagnosis of MCC. All other specimens labeled left eyebrow, upper lip, right ear, and left ear showed infiltrating moderately differentiated SCCs on a background of marked solar elastosis. Further investigations were performed to evaluate the spread of the tumor. The patient had no evidence of local bone destruction (Fig. 3a), draining node involvement or occult systemic metastases at the time MCC was diagnosed as demonstrated by CT scan (head/neck, lungs), ultrasound of the thyroid and abdomen, PET-CT scan of the lymph nodes, MRI of the brain, biopsy of the lymph node from the regional nodal basin, and the ophthalmological examination. Consequently, MCC was interpreted as stage II B (T_2 N_0 M_0) according to the most recent edition of the AJCC staging system [9]. Biospecimens obtained from the patient were sent overseas for MCPyV copy number detection by PCR and immunohistochemistry which did not reveal any evidence of transcripts related to MCPyV or expression of MCPyV-derived large T-antigen. Based on the HIV infection, the viral load, and the deranged CD4 lymphocyte count, the patient started HAART on a twice-daily regimen (Stavudin, Rifanovir). A radical surgical excision was performed, and a facial plastic surgeon reconstructed the surgical defect with a full-thickness skin graft. The patient was treated subsequently with adjuvant radiotherapy to the tumor bed with a planned total dose of 50 Gy divided in 25 fractions. She received only 3 sessions due to noncompliance. The patient declined further treatment as she became pregnant and elected not to have termination of pregnancy. Her general condition deteriorated drastically during the pregnancy and she had a recurrence of the tumor 5 months later with extensive lymph node involvement as demonstrated by PET-CT scanning

(Fig. 1b, Fig. 3b). She delivered a premature infant who died soon at the age of 2 months of HIV-related comorbidities. The Department of Medical Oncology was consulted regarding the use of palliative chemotherapy, but the patient declined the treatment and died several months later of liver and lung metastases.

Discussion

MCC, the eponym for primary cutaneous neuroendocrine tumor, is a rare skin cancer, particularly in Africans with OCA. Because of their light skin, affected individuals, especially in equatorial and subtropical regions of Africa, are at greater risk of developing skin cancers (SCC > BCC > malignant melanoma). Rates of skin cancers in albinos throughout Africa do not appear to be uniform, as reported by studies conducted in Tanzania, Nigeria, and South Africa [10, 11]. South African negro albinos have an approximately 1,000 times greater susceptibility for skin cancers than the local dark-skinned population [10, 11]. Convincing evidence for differences in risk among various types of albinism is lacking at present, but there may be differences related to different gene mutations. Mutations in genes encoding for tyrosinase (OCA 1A and OCA 1B), P-protein (OCA 2), tyrosinase-related protein (OCA 3), and MATP (OCA 4) have been identified [10–13]. OCA 5 phenotype has been recently reported among the members of a consanguineous Pakistani family, linked to an as yet unidentified specific gene mapped to the 4q24 chromosome region [14]. Gene mutation analysis was not performed in the index patient due to limited access to fresh frozen samples and financial constraints, but her phenotype fitted into the classic OCA 2 subtype (straw-colored hair, eyebrows, eyelashes, blue/gray eyes) which is by far the most prevalent type of OCA among South African blacks, affecting 1 in 3,900 individuals [11, 13]. Consanguinity plays an important role in various ethnic groups in the African population [11], but this was not the case in our patient. Asymmetric distribution of cancers has been observed previously, particularly in UV-exposed areas. The reason for laterality remains obscure. Up to date, 3 studies have explored the laterality in localization of MCC: an American study by Paulson V et al. (2011) [cited in 15], a Finish study by Koljoenen et al. (2013) [cited in 15] and a German study by Gambichler et al. [15] (2017). In accordance with the results of these studies, we also observed left localization of the tumor in our patient, an area generally less exposed to the sun in South Africa when travelling by vehicle. Thus, we consider the possibility of other than UV-related mechanisms to explain this left/right asymmetry in MCC incidence. According to Gambichler et al. [15], two transforming growth factor-beta-related proteins, Nodal and Lefty, are asymmetrically expressed and are believed to play a role in this asymmetry. While Lefty is an essential candidate regulator of early human embryonic stem cells, the expression of Nodal is restricted to the left side of the lateral plate mesoderm, of which dermis and subcutaneous tissues derive (Shriatori and Hamada, 2014) [cited in 15]. Though Nodal is inactive in most adult tissues, its re-expression and signaling are considered to drive the tumor growth [15]. The clonal integration of MCPyV DNA into the host genome in the majority of MCCs occurring in the Northern hemisphere was demonstrated by Feng et al. [16] in 2008. This observation paved the way for further research, stressing the importance of this virus in the etiology of MCC. It is believed that MCPyV drives oncogenesis through expression of the early transforming gene, i.e., small T- and large T-antigen, and their interference with several signaling pathways [2, 3, 17].

Interestingly, in MCPyV-negative tumors, several of these pathways are altered by genetic mutations, e.g., in TP53, RB1, NOTCH1–4, FAT-1, PRUNE-2, linked to UV signature events [13, 17, 18]. The presented patient fits within the latter scenario as we could not detect MCPyV

DNA or protein expression of the large T-antigen in the tumor, while showing signs of severe UV damage. The most common retroviruses associated with human cancer are the complex retroviruses such as HIV and HTLV-1/2 [19, 20]. They have spread particularly in the tropical and subtropical regions. HIV type 1 further has a direct pro-oncogenic effect, promoting the development of cancers induced by other viruses [20]. It has been reported that MCCs occur at an earlier age, on non-UV-exposed sites, have an unusual clinical presentation, and spread more rapidly in HIV-infected individuals [19, 21]. Satellite metastases can occur early or may be the first presentation. People with HIV-associated immune suppression have a relative risk of 13.4 for developing MCC compared to the general population [19, 20]. To our knowledge, there are no case studies in the English literature addressing the coinfection of HIV and HTLV-1 among sub-Saharan African albino patients. Whether MCC is more frequent in this setting has not been evaluated, but it is assumed that HTLV-1 acts as a co-carcinogen. We could trace a single case of MCC associated with multiple BCCs in an African albino woman, a refugee from Angola with HIV infection [21]. MCC has been observed contiguous to or intermingled with other skin malignancies, especially SCCs. This is particularly true for African albinos in whom reported incidences of concurrent MCC and SCC range from 5 to 34% [22, 23]. The association of MCC with SCC in combined tumors may be indicative for both an immunosuppressive state as well as chronic UV exposure. It is well established that the majority of combined tumors arise on actinically damaged skin of elderly Caucasians with a history of multiple SCCs and immunosuppression [22, 23]. Young African albinos may fit in this category due to their light skin and sensitivity to the sun, especially when associated with underlying diseases causing immunosuppression. Growing data support the likelihood that combined MCC and SCC tumors have a distinct UV-associated highly mutated genetic profile [22]. Moreover, MCCs admixed with SCCs are consistently negative for MCPyV [22, 23]. In this patient, the immune reconstitution by HAART along with surgery and radiotherapy may have initially helped to control the locally advanced MCC, but once pregnancy was further impairing the immune status, it may have caused tumor recurrence and progression. We observed in this case that survival following the diagnosis of MCC was impaired by localization of the tumor on the head, lymph node involvement, the immune dysfunction caused by HIV/HTLV-1 coinfection, and tumor characteristics (growth pattern in sheets, deep soft tissue spreading with lymphovascular involvement, minimal intratumoral infiltration of $CD8^+$ T-cells, strong positivity for Ki67, and high mitotic rate).

Although major advances have been made recently in the understanding of the carcinogenesis and immunology of MCC [1, 2, 17], large gaps still remain with regard to reliable biomarkers and prognostic indicators. Several biomarkers such as PDGF receptor, C-kit (CD117), and PI3K are overexpressed in MCCs and may be linked to worse prognosis. Other biomarkers including PD-L1, p-63, VEGFR, Ki67, CD34, some hedgehog pathway proteins, and matrix metalloproteinases have been suggested to predict disease outcome in patients with MCC [9, 24]. We checked these markers in the index patient and found that their values were consistently high from presentation (stage IIB) to late metastatic disease (stage IV).

Capsule Summary

The case presented in this report highlights the multifactorial origin of primary MCC. Various risk factors contributed to its development and rapid progression (genetic predisposition OCA2, chronic sun exposure, immune suppression by HIV/HTLV1 coinfection, and pregnancy). Head and neck localization in the setting of immunosuppression increased both

oncological and reconstructive challenges. The case reported herein in its complexity demonstrated the aggressive behavior of this tumor particularly in the African albino population and the devastating impact of immunosuppression, pregnancy, and premature discontinuation of treatment. One cannot emphasize enough the importance of early diagnosis by dermatological screening in cases of high index of suspicion and targeted services involving a multidisciplinary approach, particularly in immunosuppressed albino patients in sub-Saharan Africa. The rarity of MCC precludes the prospective, randomized clinical trials necessary to elucidate optimum treatment protocols. A multidisciplinary consensus has established treatment guidelines that are periodically updated. While surgery and radiotherapy can achieve high rates of local control, chemotherapy rarely provides a durable response for distant metastatic disease. As MCC is highly amenable to immunotherapy, immune checkpoint inhibitors addressing the PD-1/PD-L1 axis can control the disease in more than half of the patients with either virally or UV-associated MCC.

Statement of Ethics

The patient gave us written informed consent to perform all necessary investigations, to take clinical photographs, and use them for research purposes and publication.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

D. Tenea provided the clinical case, performed the clinical work and case management, and drafted the article (conception and design).

J. Dinkel analyzed the histopathology slides, immunohistochemical stains, provided the microphotographs, and made comments for Figure 2a–f.

J.C. Becker did PCR and immunohistochemistry studies for detection of MCPyV. He participated in the article design and coordination.

E. van der Walt helped in diagnostic staging and contributed to Figure 3a, b comments.

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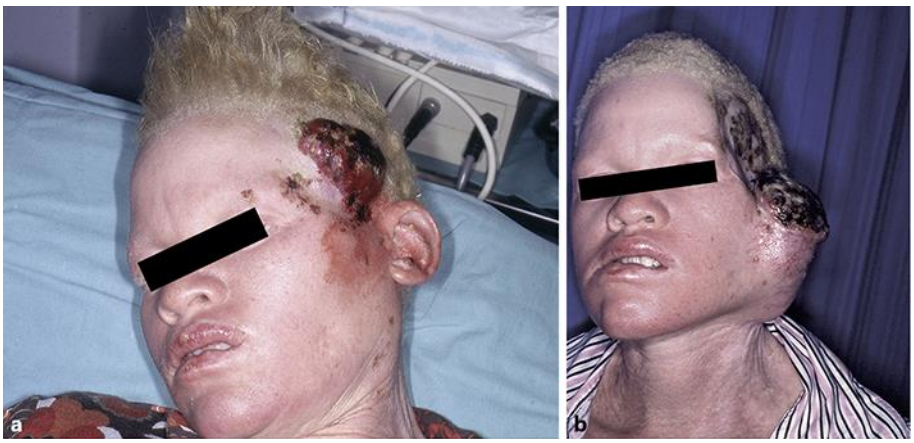

Fig. 1. **a** Dome-shaped purplish tumor on the scalp with focally hemorrhagic surface. **b** Tumor recurrence during the pregnancy invading the scalp and neck lymph nodes.

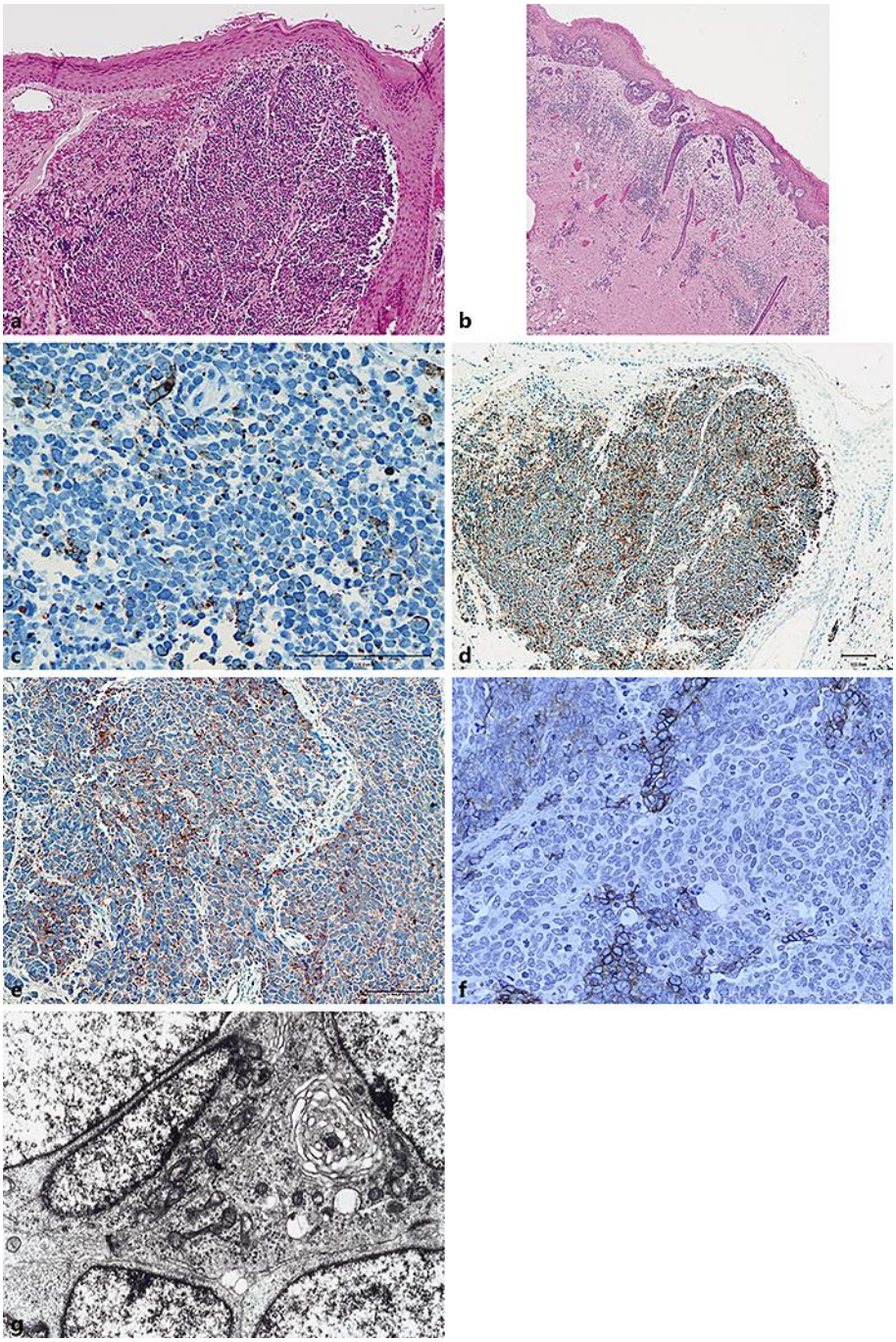

Fig. 2. **a** Extensive dermal invasion by MCC. A vaguely nested to more sheet-like growth pattern is seen (hematoxylin and eosin). **b** Associated multicentric, moderately differentiated keratinized SCC (hematoxylin and eosin). **c** Dot-like positivity for CK20 (original magnification ×40). **d** Extensive positivity for synaptophysin stain (original magnification ×20). **e** Variable positivity for neuron-specific enolase stain (original magnification ×40). **f** Positive CD56 staining intensely and diffusely labeling cell membranes of tumor cells (original magnification ×40). **g** Neurosecretory granules of the tumor cells illustrated on electron microscopy.

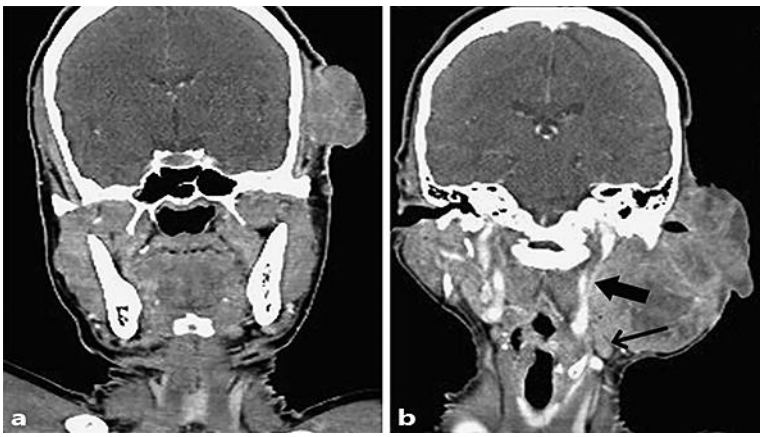

Fig. 3. **a** Primary tumor: coronal post-contrast image with left scalp mass confined to the soft tissues. **b** Recurrent tumor: coronal post-contrast image demonstrating a new nonhomogeneous mass in the left preauricular/parotid area, adjacent and inferior to the previous lesion site. Left level IV cervical lymph node is present (thin arrow). Left jugular vein displacement (thick arrow).