Merkel Cell Carcinoma in a 65 year-old Filipino: A Case Report

Abstract

Merkel Cell Carcinoma (MCC) is a rare aggressive tumor known to be metastatic to the lymph nodes with a poor prognosis. It is commonly characterized as a painless rapidly enlarging papule or nodule, which may be skin-colored, erythematous to violaceous. Being twice as uncommon as melanoma, it is seen among Caucasian elderly males. A case of a 65-year-old male, known hypertensive with chronic kidney disease, with a sudden enlargement of a painless nodule (2 x 2 x 1 cm) over the left temple is presented in this report. Initial histopathologic finding was lymphoma, however due to its rapid enlargement further work-up with immunohistochemical stains done confirmed the diagnosis of MCC. The development of MCC in a Filipino is rare and its detection requires a high index of suspicion. Upon referral to plastic surgery and radiation oncology, wide local excision and adjuvant radiotherapy were advised respectively. A wide local excision with margin control and subsequent skin-grafting was done. Thirty-three sessions of radiotherapy was advised however patient refused the suggested adjuvant treatment. Absence of nodal involvement and metastasis were documented with CT scan of the head, neck and abdomen showing no signs of adenopathy.

Introduction

Merkel Cell Carcinoma (MCC) is an uncommon, highly aggressive cutaneous neoplasm. The tumor is most often asymptomatic but rapidly enlarging which may have tendency for regional and distant nodal involvement. It is commonly seen among elderly Caucasians with immune suppression and known exposure to ultraviolet radiation. There is another etiology where in the Merkel Cell Polyomavirus (MCV) was shown to infect 80% of these carcinomas. Tumor clonal expansion of tumor cells was said to be preceded by MCV infection and integration. With this, lesions are most commonly seen in the head and neck and sun exposed areas of the extremities. A reported annual incidence of MCC in the US was noted to have increased for 25 years from 0.15 per 100,000 to 0.44 per 100,000 [1]. Being a rare but lethal neoplasm, MCC is usually mistaken for a different cutaneous malignancy until proper work-up has been made [2]. MCC requires aggressive management as it has a high rate of recurrence and often has spread to the regional lymph nodes at the time of diagnosis. A case of a 65-year-old male, known hypertensive with chronic kidney disease for 3 years, with a sudden enlargement of a painless nodule over the left temple is presented in this report. Initial histopathologic finding was lymphoma where immunohistochemistry done showed findings consistent with MCC. Treatment with wide local excision with margin control with post-excision skin grafting was done. Subsequent CT scan of the head, neck and abdomen were also done to note for regional and distant involvement and metastasis.

Case Report

This is a case of a 65-year old male, who presented at our institution due to a solitary erythematous annular plaque over the left

Journal of Clinical & Investigative Dermatology

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temple. About two months prior to consult, patient noted a painless, non-pruritic erythematous plaque over his left temple. Consult done at our institution where a 4 mm punch biopsy was done. Histopathologic findings showed a flattened epidermis with diffuse infiltrates from the dermis extending to the subcutaneous layer. This was initially diagnosed and read as lymphoma. Two weeks later, still asymptomatic, a sudden enlarged erythematous nodule (2 x 2 x 1 cm) with telangiectasia was noted over the biopsy site (Figure 1). A repeat biopsy was done and review of the previous biopsy was done. Histopathologic reading showed a dome shaped asymmetrical nodule with flattened epidermis. In the dermis are nodules of different sizes and shapes consisting of neoplastic cells of round blue cells with scanty cytoplasm and irregular nuclei closely spaced in sheets and trabecular pattern. Nuclear chromatin is dense and uniformly figures and nuclear fragments are seen per power field (Figures 2-4). Immunohistochemical stains were done which showed negative CD 3, CD 20, CK 7 and positive CK 20 (Figures 5-8). These findings were noted to be consistent with merkel cell carcinoma.

Review of systems showed anorexia. On physical examination, blood pressure was elevated at 140/80 mmHg. The rest of the systemic findings were unremarkable. The patient has comorbidities of hypertension, chronic kidney disease and benign prostatic hyperplasia for 3 years where patient is compliant with his maintenance medications. He previously had hemorrhoidectomy about 10 years prior and he just previously had an arteriovenous fistula graft creation over his right arm. However, no hemodialysis has yet been initiated. Patient has no previous malignancies with no known family history
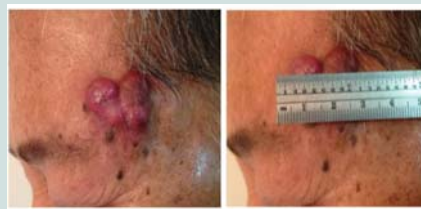

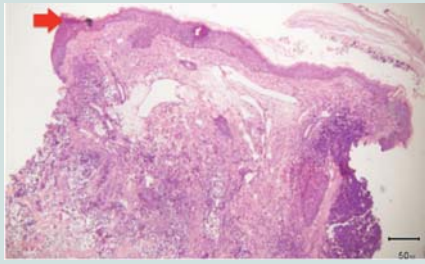**Figure 1:** A solitary erythematous nodule over the left temple.

Figure 2: Initial punch biopsy showing a flattened epidermis with diffuse dermal infiltrates.
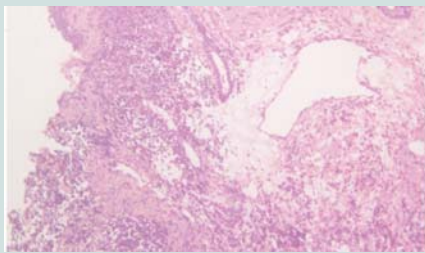

Figure 3: Closer magnification showing nodules of different sizes and shapes. It consists of neoplastic cells of round blue cells with scanty cytoplasm and irregular closely spaced sheets and trabecular pattern.
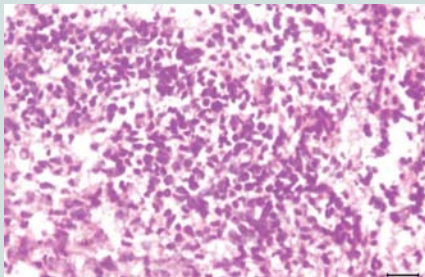

Figure 4: Aggregates of atypical cells with numerous mitotic figures. These atypical cells consist of atypical nuclei with granular nucleoplasm. Nuclear chromatin is dense and uniform figures of nuclear fragments are also seen.
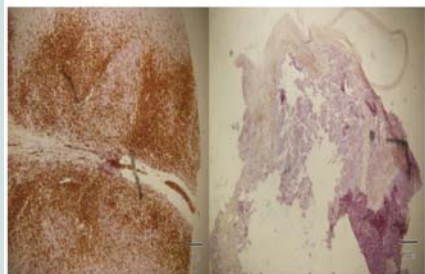

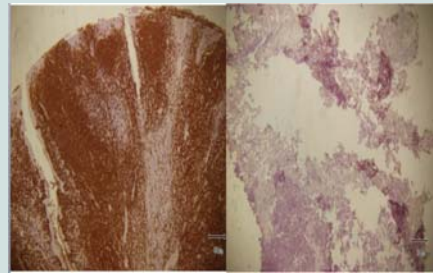**Figure 5:** Staining for CD 3 with negative result.

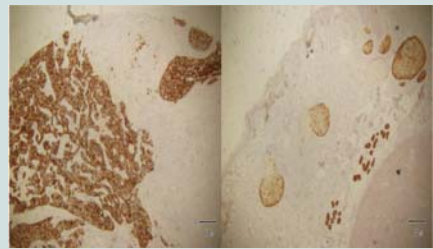**Figure 6:** Staining for CD 20 with negative result.

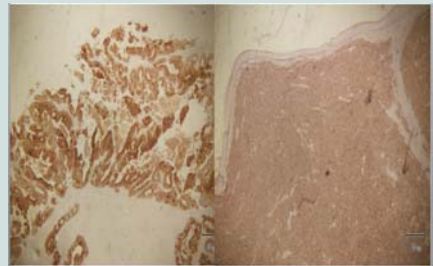**Figure 7:** Staining for CK 7 with negative result.

Figure 8: Staining for CK 20 with positive result.

Figure 9: Wide local excision done over the left temple.

as well. The patient is a retired bank teller, with occasional intake of alcoholic beverage and 24.5 pack years of cigarette smoking. Upon initial laboratory work-up, complete blood count showed anemia, proteinuria on urinalysis and elevated serum creatinine, which may be attributed to the patient's kidney disease.

Immediately after release of histopathologic results, patient was referred to plastic surgery and radiation oncology. The plan was to do wide local excision and 33 sessions of post-excision adjuvant radiotherapy. A wide local excision with adequate margin control was carried out. Review of margins histopathologically showed negative for neoplastic cells (Figures 9-12). A skin graft taken from the patient's anterior thigh was placed over the excised area. Good wound healing was noted over the grafted site one month after (Figure 13). Subsequently CT scan of the head, neck and abdomen was requested
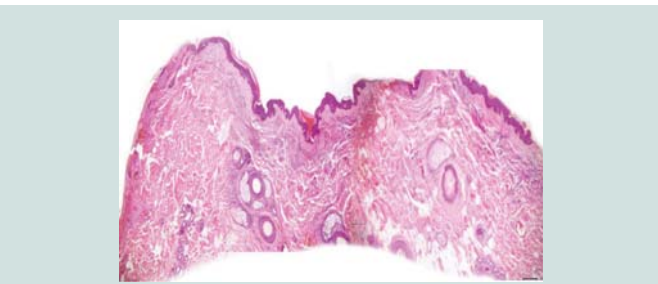
Figure 10: Immediately post-excision.

Figure 11: Post-excision specimen with negative margins.
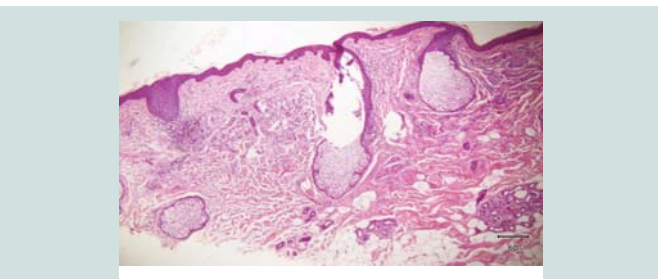

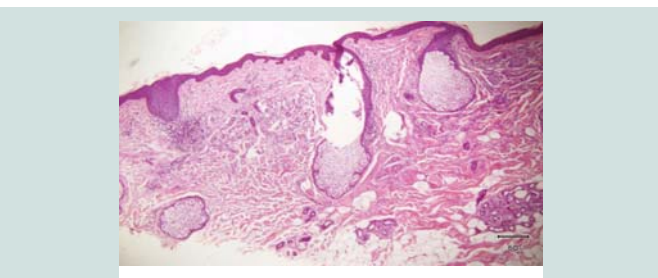**Figure 12:** Margins of the excised area showing intact adnexae.

Figure 13: The excised area 1month after skin grafting showing good wound healing.

which also showed negative lymph node involvement or any sign of metastasis. With the result, patient opted to defer the contemplated radiotherapy. Seven months after the excision, patient still claims

to have good wound healing of the graft with clinically no signs of recurrence (Figure 14-16).

Discussion

Being located in the stratum basale of the epidermis, merkel cells appear as clear cells that maybe round to oval, elongated or flattened on light microscopy. It is known to function as a receptor of mechanical stimuli, specifically sense of touch and hair movement. The origin of merkel cells has always been of debate. In one hypothesis, it has been said that similar to the melanocyte, the merkel cell has migrated from the neural crest. This is based on the association of Schwann cells to the developing fetus. In an alternate hypothesis, merkel cells were said to originate from the epidermis as modified keratinocytes. To support this, desmosomes with keratinocytes within merkel cells has been documented [3]

The first case of Merkel Cell Carcinoma (MCC) has been described by Toker in 1972 and was previously termed trabecular carcinoma [1,2]. Also known as primary neuroendocrine carcinoma of the skin, primary small cell carcinoma of the skin and cutaneous apudoma, merkel cell carcinoma is a malignant proliferation of anaplastic cells associated with a high recurrence and poor prognosis [4]. In the US, its annual incidence has increased from 0.15 cases per 100,000 to 0.44 per 100,000 in the last 25 years. In the Netherlands, it constituted 0.7% of all non-basal cell carcinoma skin cancer. The European standardized rate on the other hand was 0.3 per 100,000 person-years from 2001 to 2005 [1]. In Asia, much fewer cases have been documented to date. In a study done in Mainland China, only 22 cases were seen from 1970 to 2009. In the country, a case report done in this institution has been documented in 2009 where a patient developed MCC over the gluteal region. MCC is usually seen among elderly Caucasian males with immune suppression. The most common sites affected are the head and neck with also a predilection for sun-exposed skin. The etiology
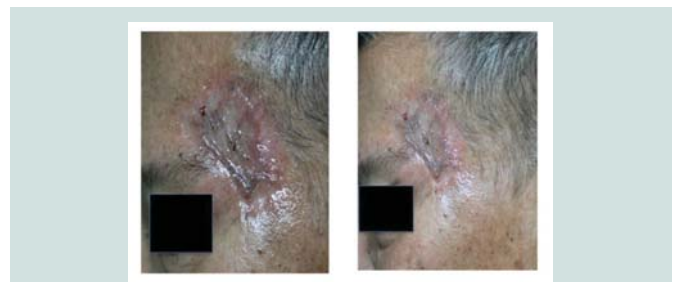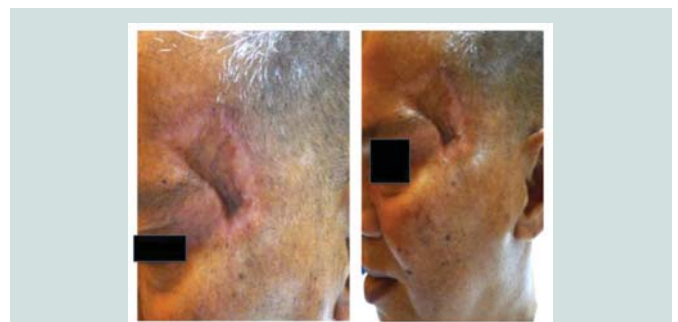

Figure 14: Threemonths post-excision.

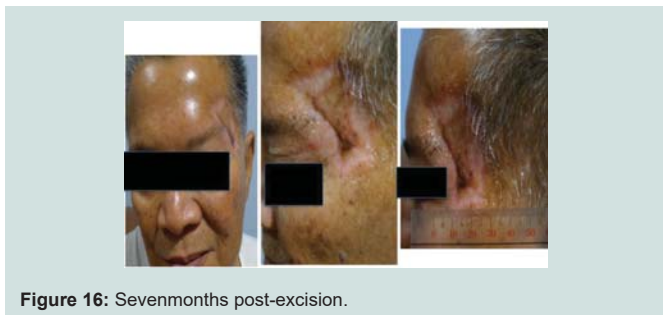**Figure 15:** Fivemonths post-excision.

Figure 16: Sevenmonths post-excision.

of MCC has yet to be determined although multifactorial associations have been determined. Ultraviolet B (UVB) radiation exposure has been noted to correlate with the disease development where people living in Hawaii, where UVB index is highest, have shown the highest incidence of MCC. Another factor is immune suppression and MCC development. Cases have been reported in patients with autoimmune disease also after solid-organ transplantation, like the kidney, liver and heart. Patients with acquired immunodeficiency syndrome also have an increased risk [1]. Recently Houben et al. have discovered a possible viral etiology that may contribute to the development of MCC [5]. A polyomavirus, now referred as the Merkel cell polyomavirus was shown to infect 80% of these carcinomas. They found viral DNA integration within the tumor genome in a clonal pattern. It was suggested that MCV infection and integration preceded clonal expansion of tumor cells [4,6,7]

MCC typically presents as a painless, pink-red to violaceous, firm dome-shaped nodule with rapid enlargement. Its surface may be shiny or may show telangiectasia. To summarize the clinical features most commonly associated with primary MCC the acronym AEIOU was developed: asymptomatic or nontender, expanding rapidly, immune suppressed, older than 50 years, ultraviolet-exposed fair skin [8]. Common differential diagnoses include basal cell carcinoma, squamous cell carcinoma, amelanotic melanoma and adnexal tumor. Because of its violaceous to hemorrhagic appearance, the differentials may also include pyogenic granuloma, abscess, angiosarcoma and lymphoma. Histopathologically, the tumor appears as a poorly defined dermal mass, with frequent infiltration to the subcutaneous fat, fascia and muscle. The edge of the tumor shows a trabecular infiltrating pattern and is composed of monotonously uniform, small round to oval cells that are about two times larger than lymphocytes. The nuclei appear finely granular dispersed chromatin in a majority of tumors. Mitotic figures are numerous usually numbering to about 5-10 per high power field. Nucleoli are usually not seen or not prominent. With immunohistochemical stains to aid in the diagnosis, there is a characteristic perinuclear globule upon staining for low-molecular-weight Cytokeratins (CK) such as CK 20, CK 5/6 and CK 7. Reportedly CK 20 is the most sensitive and specific marker for detecting micrometastases in sentinel lymph node biopsies. Staining for various neuroendocrine markers can be added where MCC will show positive staining for chromogranin, synaptophysin, somatostatin, calcitonin and vasoactive intestinal peptide. With the recognition of Merkel cell polyomavirus, immunohistochemical and molecular biologic methods can provide additional tools for diagnosis. Electron microscopic studies of carcinoid, neuroendocrine, and primary Merkel cell carcinomas show "neurosecretory" membrane-bound, dense-core granules measuring 100 to 250 nm in diameter [4-6,8]

The American Joint Committee on Cancer staging system is similar to the 4-tier system from the Memorial Sloan-Kettering Cancer Center. The said MCC staging system is based on tumor size, lymphatic spread, and distant metastasis. The 4-tier staging includes the following: stage I for primary lesions <2 cm, stage II for primary lesions >2 cm, stage III for positive lymph nodes and stage IV for those with distant metastasis. The staging is used to determine the appropriate treatment and to predict disease prognosis. A 10-year relative survival rate is correlated to the tumor size and is 61% for patients with tumors < 2 cm and about 40% for patients with tumors >2 cm. A recurrence rate of 40% has been reported [4,6]

For the treatment, surgery is still the primary approach. In a study by Fields et al, they have reviewed recurrence after complete resection and the selective use of adjuvant therapy for Stage I through III MCC. A low recurrence rate in patients with clinically lymph node-negative MCC can be achieved with adequate surgery and that the selective use of adjuvant radiotherapy is recommended for high-risk tumors [9]. In an evidence-based review of the management of primary and localized MCC by Ellis et al, the mainstay of approach for newly diagnosed MCC remains surgical. Their current recommendations are based on the size of the primary tumor and excision with 1cm margins. Some studies have suggested a 2cm margin. But since most of the lesions are located in the head and neck, the aesthetic and functional outcomes of surgery must be considered where a smaller margin is recommended. The use of Mohs micrographic surgery is still a relatively new modality and that its benefit over wide local excision include tissue conservation [10-12]. It has been shown to be as efficacious as wide excision in treating localized MCC. There have also been enough data to advocate the use of adjuvant radiotherapy owing to the high incidence of recurrence and metastasis. Adjuvant radiotherapy has been of greatest benefit in improving the survival of cases where tumors were >2 cm. However, there is little evidence that suggested that the use of radiotherapy in those with histologically negative margins in reducing local recurrence rates. When used as monotherapy, radiotherapy is only used when in inoperable cases. Chemotherapy is only reserved for systemic disease and with very limited success, no chemotherapy protocol has yet been shown to increase survival [8,13,14].

Conclusion

Merkel cell carcinoma presenting in an elderly Filipino male over a period of less than 3 months is relatively rare. Early diagnosis and management is key to the control of the disease as it is a highly aggressive neoplasm with a propensity for local recurrence. A high index of suspicion is also key to the early detection of the disease. One must keep in mind the clinical AEIOU's of MCC, which include: asymptomatic or nontender lesion, expanding rapidly, immune suppression, older than 50 years and ultraviolet light exposure. Appropriate work-up must be done such as immunohistochemistry to confirm the diagnosis. For localized MCC, surgical excision is still the treatment of choice. Additional adjuvant radiotherapy must be highly considered especially for more advanced stages of the disease at diagnosis. The use of skin grafting may also be of benefit in providing tissue conservation. Evaluation for regional and distant metastasis along with close follow-up must be done accordingly to improve survival.

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