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MERKLE CELL CARCINOMA OF LEFT FOREARM: A CASE OF RARE SKIN TUMOR

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ABSTRACT
Merkel cell carcinoma (MCC), also known as the primary cutaneous neuroendocrine neoplasm of the skin is a highly aggressive tumor that commonly occurs in exposed areas of the body, especially at the head, neck, and extremities in elderly patients. This rare cancer originates from Merkel cells; the cells usually found at dermo-epidermal junction with neuroendocrine characteristics. In the United States, the approximate incidence of Merkel cell carcinoma is very low but the overall prognosis of MCC is not favorable. The only treatment options available for MCC are wide local surgical excision and Mohs microscopic surgery if indicated by anatomical factors. For nodal disease and postsurgical, adjuvant radiotherapy and chemotherapy also recommended for a better outcome and decreased the chances of reoccurrence. However, despite the available treatment modalities for MCC, at present new treatment options and strategies are under investigation.

KEYWORDS: Markel cell carcinoma, Neuroendocrine tumor, Rare Skin tumor.

INTRODUCTION
Merkel cell carcinoma, first presented in 1972 by Toker, is an uncommon, highly aggressive malignant neoplasm of skin arising from Merkel cells.[1,2] It is a unique cutaneous neuroendocrine cancer of the skin that has lately been identified as a distinct clinical and histopathological entity of cancer. MCC is very aggressive and arises from chronically sun-exposed areas of head, neck, and extremities in elderly patients. It most commonly occurs as small cell cancer in the skin, and clinically characterized by local combative behavior and distant metastases, similar to other small cell cancers originating from the lung, cervix, and other sites.[2] Merkel cells, located at the dermo-epidermal junction, are postulated to be neuroactive cells of epidermal origin with neuroendocrine features. The cells are easily identified ultra-structurally by dense core granules or by immunohistochemical methods.[3]

The five-year overall survival rate has been calculated at 45% regardless of the accessibility of appropriate treatment.[4] Although the case mortality rate is remarkable, the frequency of MCC in the United States is low, estimated at 0.24 cases per 100 000 per year contrasted with melanoma (17.0 cases per 100 000 per year), a 70-fold deviation.[5] Merkel cell carcinoma imparts with melanoma the strong tendency to re-emerge locally, disseminates regionally to the lymph node, and spread widely, prompting a lethal outcome. In contrast to melanoma, there is evidence that Merkel tumor cells might be profoundly radiosensitive.[6]

Exact staging combined with co-ordinated multidisciplinary treatment is fundamental to dispensing the optimal care to patients with MCC.[7] Surgery keeps on being the suggested primary modality of treatment with wide local excision with clear margins when possible, and specific neck dissection when needed. Mohs micrographic surgery has been designed as an option in contrast to wide local excision, and the current guidelines recommend this as a substitute if indicated by anatomic factors. For certain nodal disease and postsurgical adjuvant radiation are commonly indicated and have been appeared to improve results and hence are suggested by the current guidelines.[8]

Case presentation
Here we present the case of Merle Cell Carcinoma. The patient was sixty-eight year-old, male presented with painless left forearm exophytic nodule that was progressively increasing in size as described by the patient. The patient denied any significant history of similar illness in the past. Past medical and surgical history was unremarkable. There were no associated

other symptoms, and the patient was feeling fine. Multiple different laboratory tests were performed, and no abnormal values were reported. The patent underwent local excision of the nodule, and the gross specimen was submitted for histopathology evaluation.

A dermal based lesion extending to the low margin was seen. Round blue cells with the nuclear crushing artifact, high nuclear-cytoplasmic ratio, a granular nucleus with some nuclear clearing, and few lymphocytic infiltrate, as shown in “figure 1, 2”. The immunohistochemistry stain cytokeratin 20 (ck20), showed perinuclear dot staining which is "essential for the diagnosis of Merkel Cell Carcinoma" “figure 3”. To rule out the melanoma and rule in carcinoma, cytokeratin stain showing positive results in “figure 4”. Immunohistochemical stain showing positive neuroendocrine markers; Chromogranin and Synaptophysin “figure 5, 6”. Negative TTF1 and P40 stain to rule out the small cell carcinoma (SCC), and squamous cell carcinoma (SCC), respectively, as shown in “figure 7, 8”.

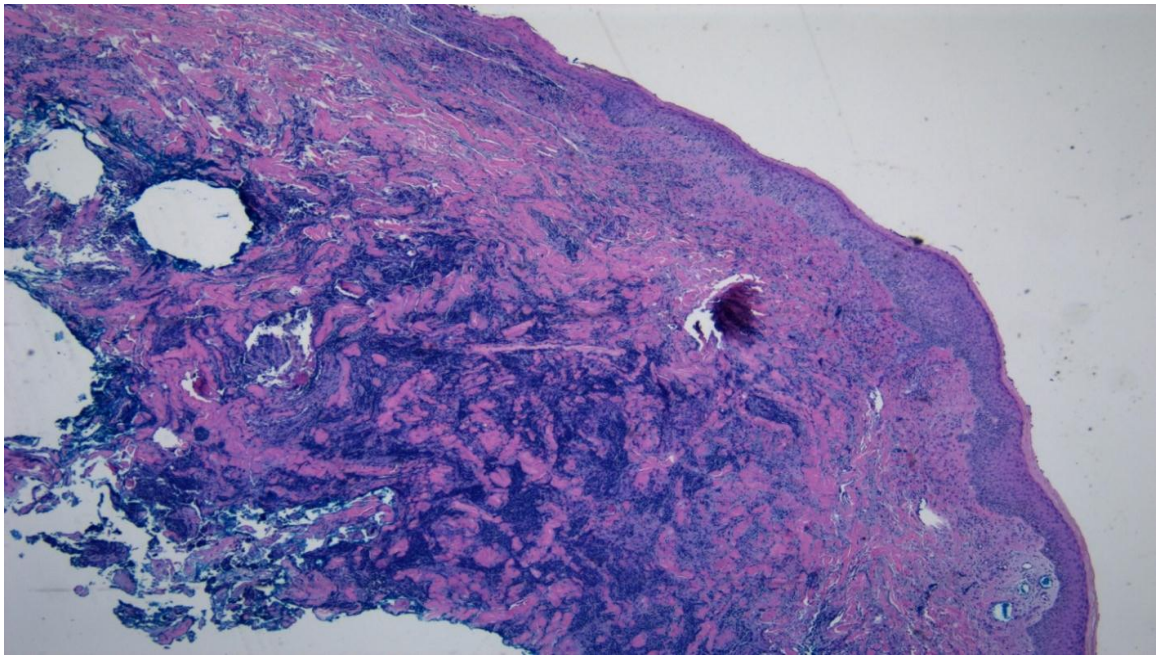

Figure 1: H&E stain, low power. A dermal based lesion extending to the deep margin.

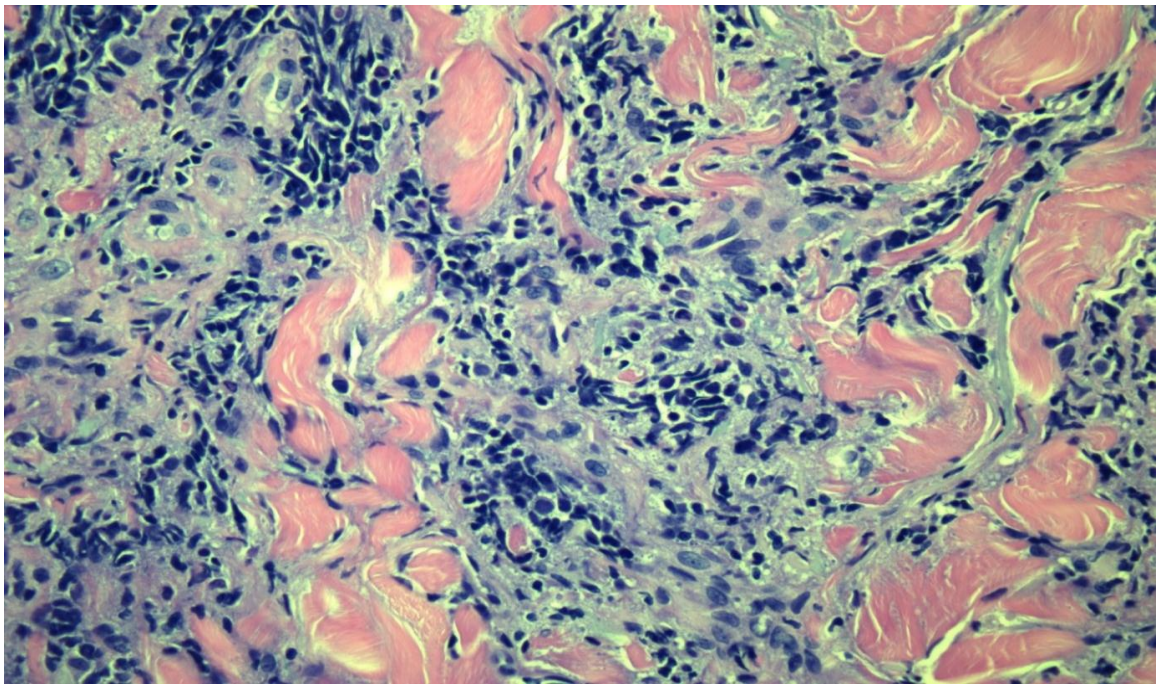

Figure 2: H&E stain, high power, high nuclear: cytoplasmic ratio, granular nucleus, nuclear clearing and few lymphocytic infiltrates.

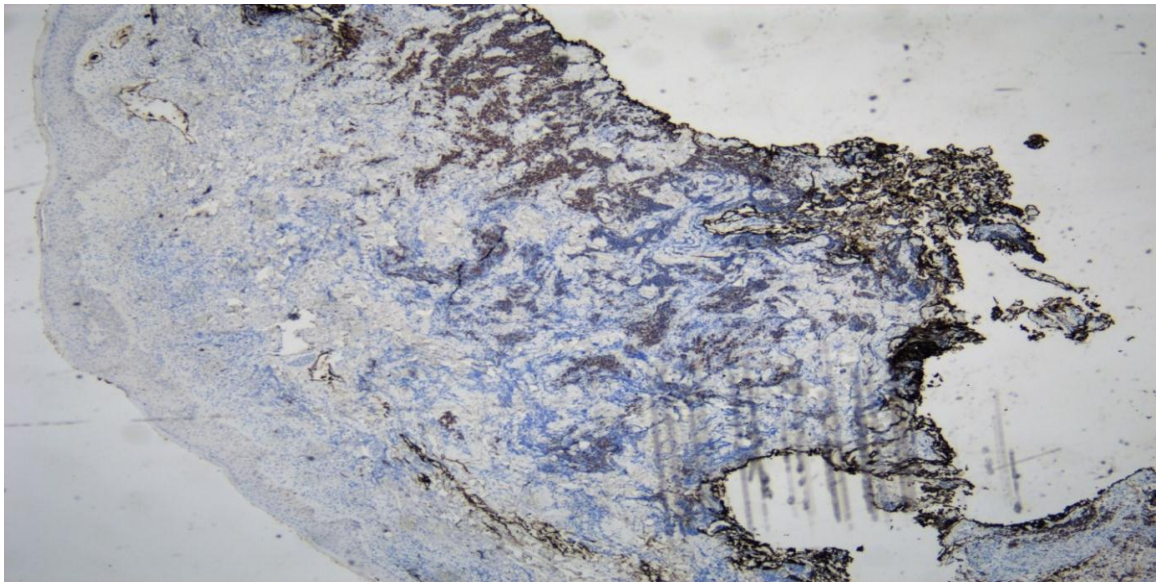

Figure 3: Positive CK20 showing perinuclear dot staining.

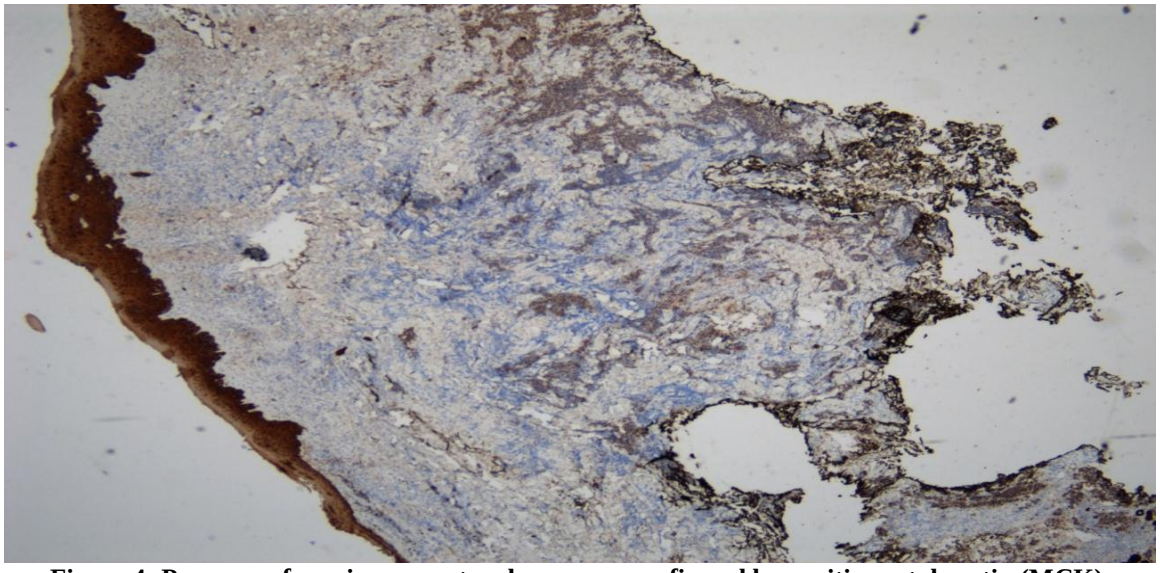

Figure 4: Presence of carcinoma, not melanoma as confirmed by positive cytokeratin (MCK).

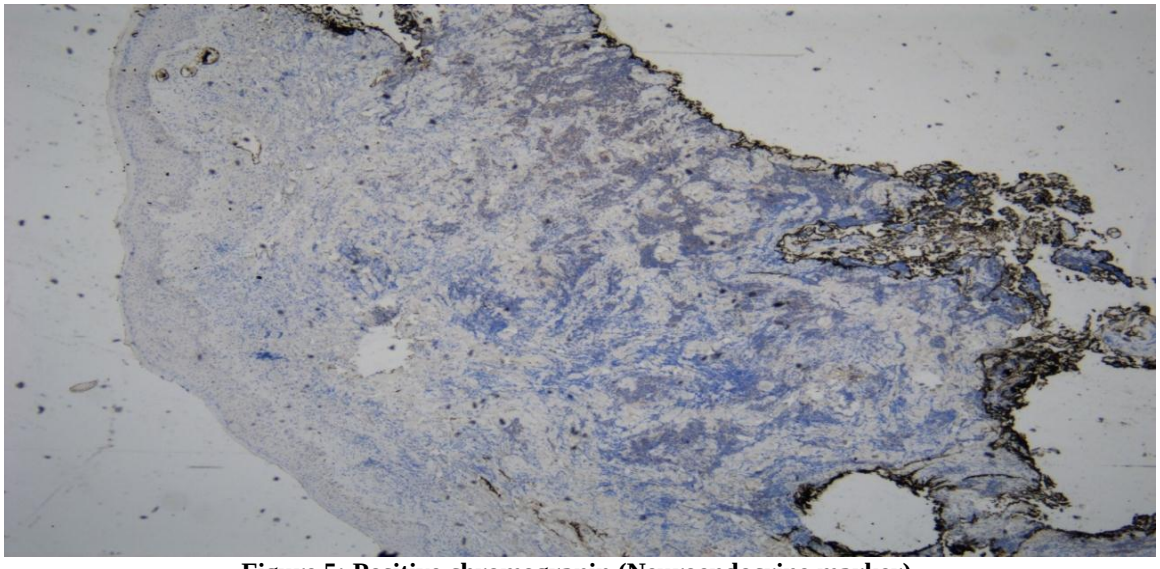

Figure 5: Positive chromogranin (Neuroendocrine marker).

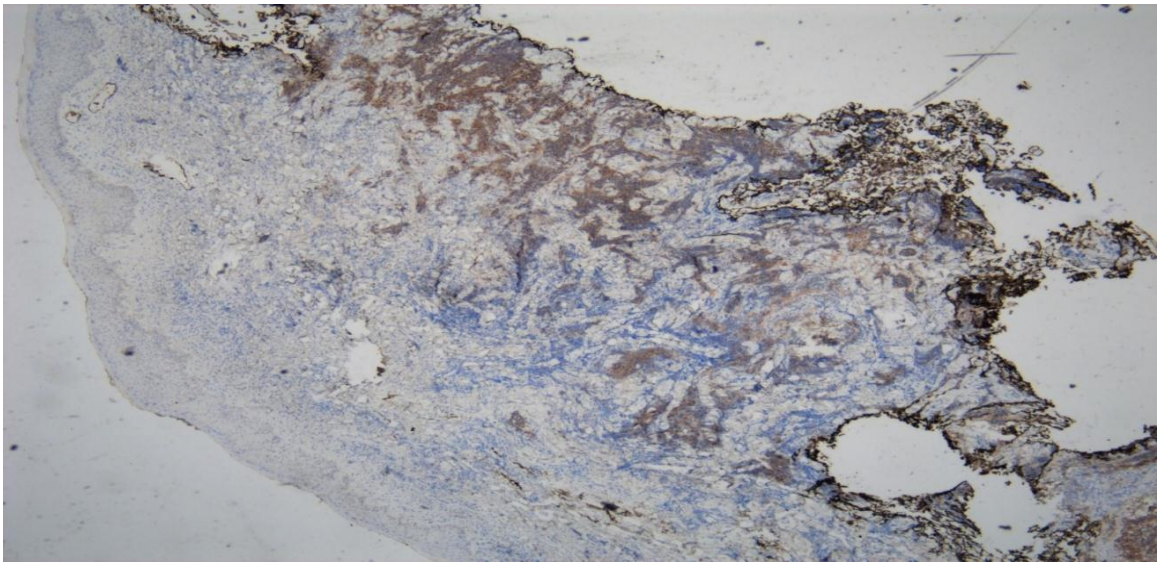

Figure 6: Positive synaptohysin (Neuroendocrine marker).

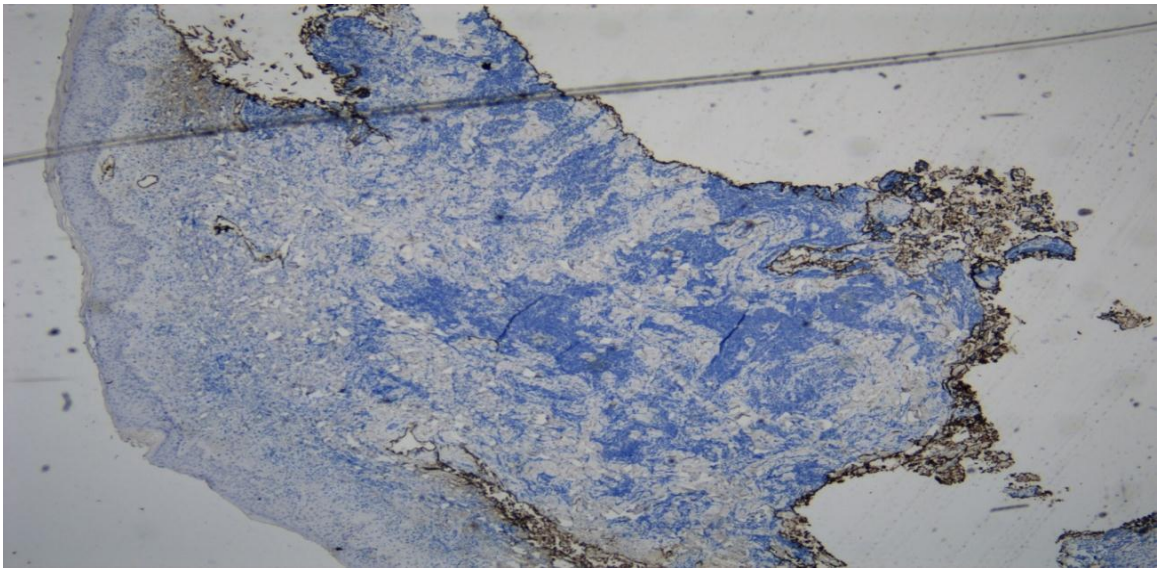

Figure 7: TTF1, Negative stain ruled out the small cell carcinoma.

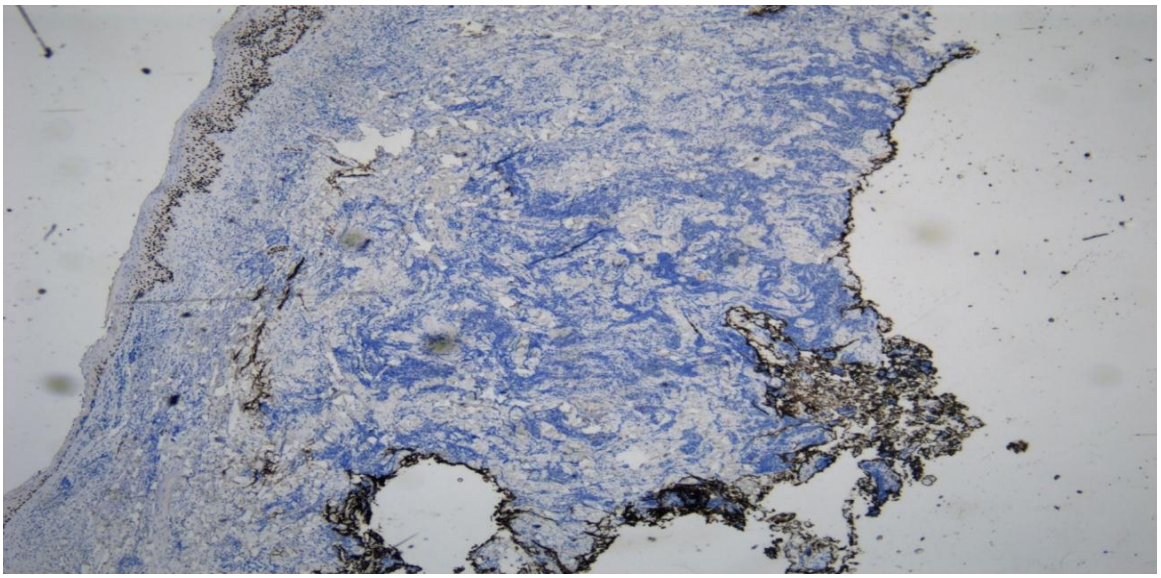

Figure 8: P40, Negative stain rule out the squamous cell carcinoma.

DISCUSSION

Merkel cell carcinoma is an aggressive neuroendocrine neoplasm of the cutis. It is unique in the United States, with an estimated 470 new cases each year.[9] It often affects the areas of the skin, which is exposed to sunlight, and commonly affected areas are head, neck, and extremities comprising more than 50% of the cases. Mainly it occurs in elderly whites with a mean age of 69 years.[10] Most of the patients have coexisting squamous cell carcinoma and basal cell carcinoma of the skin that signify similar carcinogenic factors such as ultraviolet light.[11]

The mortality of MCC appears to be primarily associated with the microscopic spread of the disease, reflecting the Halstedian model with progressive spread to the regional lymph nodes preceding hematogenous metastasis.[12] A cohort study of more than 5800 MCC patients sets out the relative survival rates of patients presenting with regional nodal disease, distant metastatic disease, and local disease.[13] Patients coming with the local disease had a 71% relative survival rate of three years after MCC been diagnosed. However, people with nodal and distant metastatic spread evidenced 48% and 20% comparable survival rates, respectively, over a similar timeframe. Primary tumor size likewise has been appeared to have a positive predictive value on endurance rates.

Moreover, patients presenting with a ≤2-cm lesion had a 74% survival rate, whereas those with a tumor sized 2.1 to 5.0 cm had a 62% survival rate. The dominant anatomical sites that develop MCC are areas often with sun exposure such as the skin of upper limb and shoulder (22%), skin of lower limb and hip (15%), and skin of the face (27%).[14] Besides, the occurrence is increased in European descent, which might be identified with the lack of defensive melanocytes. With a high number of Merkel cells on the hand and continuous exposure to UV radiation, the probability of arising MCC on the hand is increased. Interestingly, a recent case report showed the connection of radiation exposure with MCC in a senior surgeon who often performed digestive tract radiography with the uncovered hand.[15] The chronic exposure to radiation may have added to the advancement of MCC with squamous cell carcinoma in situ. Albeit uncommon, MCC has additionally been found inconsistently on the penis, vulva, and in the parotid organ.[16]

Histologically, it is difficult to distinguish the MCC from other poorly differentiated, round, blue cell tumors and need hematoxylin, eosin as well as immunohistochemical stains to do so. MCC cells commonly have a small amount of cytoplasm, prominent basophilic nuclei with powder dispersed nuclear material, and deep nuclei. Sporadically, mono-cellular necrosis, repeated mitosis, and infiltration of epithelial, lymphovascular, and perineural tissues may happen. MCC cells exhibit properties of both neuroendocrine and epithelial cells. They express epithelial markers such as AE1/AE3, CAM 5.2, pan-cytokeratin, epithelial membrane antigen, and Ber-EP4 and probably stain various neuroendocrine markers, as well as chromogranin, synaptophysin, calcitonin, vasoactive intestinal peptide, and somatostatin receptor.[17] MCC can be distinguished from other undifferentiated tumors by staining with low-molecular-weight cytokeratins (e.g., CK20, CK5/6). It shows positive results when stains with low molecular weight CK20 and also exhibit Para nuclear dot-like positive features.[18]

One investigation discovered that a novel strain of polyomavirus was involved in the growth of MCCs. This polyomavirus was presented in roughly 80% of all MCCs. Be that as it may, the specific action of Merkel cell polyomaviruses in MCC pathogenesis stay unknown.[19] Management of MCC, later on, should concentrate on explaining the viral causes of tumors also and the insusceptible guideline in light of these infections with the goal that a focused on the way to deal with treatment can be made. Following this, there are many developing treatment methodologies, for example, adopting cell immunotherapy, the simple somatostatin treatment, sign transduction blockade, and immune checkpoint inhibition.[20] MCC has many clinical similarities with different types of appendage cutis neoplasm as discussed in table 1.

Table 1: Merkle Cell Carcinoma differentiating features from different appendageal neoplasm.

Types of Cancers	Clinical Differentiating Features
Merkel Cell Carcinoma (MCC)	Flesh-colored to erythematous to violaceous, overlying scale and telangiectasia (more in UV areas), Circumscribed or infiltrative borders
Basal Cell Carcinoma (BCC)	Abundant peripheral palisading, low cuboidal to columnar cells, budding off of the epidermis, mucin, single-cell necrosis
Melanoma	Predominance of irregular intraepidermal nests, cytologic pleomorphism, irregular nuclear borders, prominent nucleoli, melanin pigment
Lymphoma	Vesicular, cerebriform, reniform or wreath-shaped nuclei, scant cytoplasm
Sebaceous Carcinoma	Crenulated nuclei, vacuolated cytoplasm, often extensive intraepidermal or intra-adnexal involvement
Squamous Cell Carcinoma (SCC)	Preponderance of squamous differentiation, in situ SCC component, clear transition between well differentiated and less well differentiated areas

CONCLUSION

Due to the aggressive nature of Merkel cell carcinoma and the tendency to metastasize distant, early diagnosis by skin biopsy and adequate surgical excision is crucial for a favorable prognosis. The treatment of MCC relies on numerous factors including but not limited to the nodal involvement stage of the tumor, location of cancer, and the distant metastasis. Currently, accessible treatment modalities are wide local surgical excision with sentinel lymph node biopsy and excision. The proper adjuvant chemotherapy and radiation are essential for nodal or distant metastatic disease. However, yearly skin examinations and continuous observation are recommended for a better prognosis.

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