Review Article

A Current Review on Merkel Cell Carcinoma and Future Management

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Abstract

Merkel cell carcinoma (MCC) is a rare malignant cutaneous neoplasm derived from neuroendocrine tactile cells in the basal layer of the epidermis. It is typically located on sun exposed areas of the elderly Caucasian population and although rare, MCC had the greatest increase in incidence of all skin cancers in the past decade. Merkel cell carcinoma has a multifocal etiology involving UV exposure, Merkel cell polyomavirus, and immunosuppression. This article reviews the presentation, pathogenesis, diagnosis, and current treatment for MCC. Future treatments involving immunotherapy and targeted therapies are also discussed.

ABBREVIATIONS

MCC: Merkel Cell Carcinoma; MCV: Merkel Cell Polyomavirus; RB1: Retinoblastoma 1; PD-1: Programmed Death Receptor-1

INTRODUCTION

Merkel Cell Carcinoma (MCC) is a rare cutaneous neoplasm, typically located on sun-exposed areas of the body in the elderly Caucasian population [1]. It is derived from neuroendocrine tactile cells in the basal layer of the epidermis and is aggressively malignant in nature [2]. Early locoregional metastasis is common in MCC with lymph node involvement present at diagnosis in 27% of cases [3]. Although rare, MCC had the greatest increase in incidence of all skin cancers from 1986 to 2001 growing from 0.15 to 0.44 cases per 100,000 people over these years; the incidence of MCC is currently estimated to be 0.79 cases per 100,000 in the United States [1]. MCC is also the most lethal skin cancer on a case-by-case basis, with one third of patient’s succumbing to the disease [4].

PRESENTATION

MCC typically presents as a red to purple, painless nodule, that rapidly enlarges on sun exposed areas of the body [5]. The lesions are usually less than 20mm, but may show a range in size from 2mm to 200mm [2]. Locations most frequently affected by MCC are the head and neck, which are involved in 48% of cases [2]. Those with MCC are typically Caucasian, with 98% of the cases involving this demographic [6]. Age also appears to correlate with prevalence of disease, as roughly 5% of MCC cases are reported before 50 years of age [2]. Although atypical, MCC may present on non sun-exposed areas of the body with an associated worse prognosis [7].

PATHOGENESIS

MCC has a multifactorial etiology involving the interplay of the following three factors: viral infection, UV exposure and immunosuppression. The Merkel cell polyomavirus (MCV) has been implicated in 80% of MCC cases and serves as a delineation point for the two subtypes of this neoplasm, MCV-positive and MCV-negative MCC [1,4]. In MCV-positive cases, the virus is theorized to integrate into the host genome and elicit its effect by encoding an oncogene, called the large T antigen [8]. The large T antigen, when phosphorylated at site S220, inactivates the tumor-suppressor RB1 thus promoting clonal expansion [8]. Additionally, the large T antigen is capable of binding to host helicase enzymes and heat-shock proteins in order to manipulate cellular function [1]. One example of this is seen in the upregulation of the molecule Survivin by the large T antigen [9]. Survivin is a potent inhibitor of apoptosis and overexpression is associated with a poor disease outcome [10]. In most virus-negative cases, there is a much higher mutation load than in virus-positive cases [4]. It is thought that the cumulative mutations from UV exposure inactivate the RB1 gene and lead to clonal expansion when the MCV large T antigen is not present [4]. The incidence of MCC is drastically higher in immunosuppressed patients suggesting that immunosurveillance is critical in halting the development and progression of MCC, whether the MCV is present or not [4].

DIAGNOSIS

Due to the relatively benign initial appearance of MCC, the clinical diagnosis is made on the basis of many factors including the patient’s history and physical exam, skin and nodal examination, and biopsy with subsequent H&E prep [11]. An immuno-panel should confirm the diagnosis and include the markers CK20 and thyroid transcription factor-1 [1]. In a majority of cases the cell
Central marker CK20 is positive while thyroid transcription factor-1 is negative, which aids in differentiating MCC from other neoplasms such as melanoma, lymphoma, or small cell lung cancer [1]. After establishing the diagnosis of MCC, further work-up is necessary to stage the disease. Local lymphatic spread is evaluated by sentinel lymph node biopsy, whereas PET-CT scanning allows for the identification and quantification of distant metastasis [12]. CT or MRI scanning may be suitable alternatives for staging purposes if PET-CT is not available; however, these modalities are not as sensitive [2]. The identification of viral status using molecular techniques such as PCR may also be beneficial in selecting specific therapies targeting MCC [12].

CURRENT MANAGEMENT

Concerning the treatment of MCC, surgical resection with negative margins is the mainstay of therapy [11]. 1 to 2cm margins in wide local excisions are the current National Comprehensive Cancer Network recommendation; however, Mohs micrographic surgery is a more progressive alternative strategy available at some institutions [1]. In addition to achieving negative margins, sentinel lymph node biopsy is a valuable tool in the staging of MCC and should be conducted whenever possible [12]. This is typically done intraoperatively during wide local excisions or preoperatively with respect to the Mohs procedure [2].

The role of radiation therapy in MCC is under investigation and somewhat controversial [13]. Studies looking at primary vs post-surgical adjuvant use of radiation have had difficulties in finding a significant difference in the survival of the two groups [14]. While radiation therapy may serve a role in patients with contraindications to surgery, its adjuvant use may only be significant in patients with stage I/II disease [2,13]. Chemotherapy, which is usually a combination of etoposide and a platinum based agent, is most often reserved for palliative therapy in those with widespread metastatic MCC [12]. MCC is commonly chemo-sensitive and initially responds well; unfortunately, most cases fail to sustain a durable response and recurrence is frequent [1].

FUTURE MANAGEMENT

The combination of MCC’s aggressive early metastatic nature and a lack of a sustained response to chemotherapeutics drive the medical community’s need for new therapeutic agents to combat this disease. Pembrolizumab is a promising new agent that uses monoclonal antibodies to target and block the cell’s programmed cell death receptor 1 (PD-1) [15]. The PD-1 receptor is expressed by cytotoxic T lymphocytes and when bound by the PD-1 ligand expressed on MCC cells leads to an inhibition of the lymphocytes ability to eliminate neoplastic cells [16]. In a phase II clinical trial
a 56% objective response rate was achieved by inhibiting this pathway and thus blocking the ability of the neoplastic cells to suppress the immune system [15]. Interestingly, and contrary to what was previously thought about immunotherapy and MCC, the MCV viral status of tumors does not influence their response to Pembrolizumab therapy [15].

Another potential therapy involves the transfer of ex vivo expanded polyclonal T lymphocytes specifically targeted to the MCV-positive tumor cells. Prior to lymphocyte transfer, the MCC lesions are exposed to either single-dose radiation or intralesional IFN-beta-1b to increase HLA-1 expression [17]. Once transferred to the body, the MCV specific lymphocytes remain in vivo for up to 3 months and preferentially localize to metastatic MCC tissue [17]. Chapius et al., noted regression in 2 of 3 detectable metastasis and a prolonged period without development of new metastasis when compared to other therapies; 535 days vs a mean of 200 days [17].

Targeting therapy towards mutations in cellular signaling pathways has been successful in the treatment of numerous neoplasms; however, most MCC tumors are MCV positive and frequently lack the particular mutations that are susceptible to targeting in the MCV negative cases [4]. Despite this setback, there has been some success in small clinical trials involving cases of MCC that are due to mutations in cellular signaling pathways. MCC with PI3K/AKT, c-kit, and mTOR mutations have all been susceptible to such therapy [18]. Additionally, YM155, an inhibitor of Survivin, has been under investigation for its potential therapeutic use. A recent study revealed that YM155 halted the growth of MCV positive MCC in xenografts [9]. Unfortunately, as soon as the drug therapy was discontinued the tumors resumed growth signifying the effect of YM155 is only cytostatic [9]. Finally, downregulation of VEGF should be explored as neuroendocrine tumors are known to be highly vascularized [2]. In those with isolated disease to the limb, there is yet another therapy on the horizon. Hyperthermic isolated limb perfusion, known for its current role in advanced melanoma, may be relevant in the discussion and treatment of MCC. Thiels et al., reported excellent local–regional control in patients with MCC in-transit metastasis [19].

PROGNOSIS

Due to recent controversy, a review of MCC staging was performed to evaluate whether clinical or pathological staging was more important. Newer studies have shown that even MCC's smallest tumors have a 10-20% risk of metastasis [20]. Therefore, an analysis of the prognostic factors was performed and showed that pathological nodal staging has a better predictive value of survival than clinical nodal staging [3]. The NCCN guidelines now recommend a SLNB be performed whenever feasible, regardless of clinical nodal stage [11]. Additionally, studies have shown a survival benefit in patients with an unknown primary lesion and a very poor prognosis in patients presenting with lesions on non-sun exposed areas [3,5].

DISCUSSION & CONCLUSION

Conclusion

Merkel cell carcinoma is a rare neuroendocrine tumor with a multifocal etiology including UV exposure, polyomavirus infection, and immunosuppression. MCC usually appears as a painless red to purple nodule on sun exposed areas of the body, although a primary lesion may not be seen at all [5]. When considering therapy, identifying the presence of the MCV virus has shown to be beneficial in guiding an approach to treatment [4]. MCV negative MCC is associated with a greater set of molecular mutations creating a more vast potential for targeted therapies [1]. The incidence of MCC in immunosuppressed patients was much higher than in the general population, implying that the immune system plays a role in the progression and development of MCC and could help guide future potential therapies [1]. Currently management involves staging the disease with sentinel lymph node biopsy for local metastasis, and use of a PET-scan or CT for distant metastasis [11]. Surgery is the mainstay of treatment with either adjuvant radiation or chemotherapy, but chemotherapy is usually reserved for patients with severe metastatic disease and these patients have high recurrence rates [1]. Clinical trials involving future therapies targeting the PD-1 receptor, lymphocyte transfer, and specific pathways of the cellular signaling of MCC are promising, but longer patient follow up and larger cohorts are needed. Based on the lack of a current effective treatment, physicians should consider tailoring therapies towards the patient’s specific mutations in order to optimize therapy.

REFERENCES

1. Cassler NM, Merrill D, Bichakjian CK, Brownell I. Merkel Cell

Figure 1 H&E staining of an excisional biopsy of MCC with positive margins (Adapted from Acab et al. [5]).


