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Merkel cell carcinoma: An algorithm for multidisciplinary management and decision-making

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ABSTRACT

Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine tumor of the skin. Therapeutic approach is often unclear, and considerable controversy exists regarding MCC pathogenesis and optimal management. Due to its rising incidence and poor prognosis, it is imperative to establish the optimal therapy for both the tumor and the lymph node basin, and for treatment to include sentinel node biopsy. Sentinel node biopsy is currently the most consistent predictor of survival for MCC patients, although there are conflicting views and a lack of awareness regarding node management. Tumor and node management involve different specialists, and their respective decisions and interventions are interrelated. No effective systemic treatment has been made available to date, and therefore patients continue to experience distant failure, often without local failure.

This review aims to improve multidisciplinary decision-making by presenting scientific evidence of the contributions of each team member implicated in MCC management. Following this review of previously published research, the authors conclude that multidisciplinary team management is beneficial for care, and propose a multidisciplinary decision algorithm for managing this tumor.

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1. Background

Merkel cell carcinoma (MCC) is a rare and highly aggressive neuroendocrine tumor of the skin. MCC incidence has tripled during the last 15 years, and the 3-year mortality rate is 33% (Prieto et al., 2013; Becker, 2010). In addition to the deleterious effects of the disease, advances in immunodiagnostic techniques have led to an increase in the number of diagnosed cases (Wong and Wang, 2010). Due to its increased incidence and the aging of the population, defining standard treatment approaches for patients with MCC will become even more important in the future. Currently, however, physicians and surgeons must interpret highly heterogeneous, retrospective literature in order to manage the disease. Multidisciplinary management is essential to determine the best therapeutic approach for these elderly and immunosuppressed patients (Prieto et al., 2013).

The aim of this multidisciplinary review is to define the contribution of the different specialists involved in MCC management and to design a decision algorithm based on the expertise of each. Increased specialization has led to the introduction of multidisciplinary teams (MDTs) for the management of cancer. MDTs seek to ensure that all patients will benefit from the knowledge of a variety of specialists, who share their expertise, professional perspective, and knowledge (Fleissig et al., 2006; Brown, 2012). These teams are usually made up of surgeons, physicians, pathologists, clinical nurses, and various therapists. Adequate documentation and staging of Merkel tumors must be based on a verbal description, accurate measurement, diagrammatic representation, photographic records, pathologic differential diagnosis, and appropriate radiologic and nuclear imaging. Therefore, the specialists included in MCC management are dermatologists, radiologists, nuclear physicians, pathologists, surgeons, and medical and radiation oncologists.

The specialist co-authors of this review have each carried out a literature review of this topic within their respective specialties. To do this, the authors used PubMed to search for articles published in journals with a high impact factor and written by authors with demonstrated knowledge of MCC, giving precedence to the most recent papers.

This review presents the scientific evidence of the contributions of each team member as collected in the literature. After studying the expertise made available within each of the different fields, the authors find substantial benefit in multicisciplinary team management and propose a decision algorithm for management of this tumor.

2. Dermatologist

Dermatologists tend to be the first clinicians who come into contact with the patient and initiate the first diagnosis. However, depending on the country and even on the patient work-flow, general practitioner is the first professional that faces the patient. In any case, the well informed first physician should take the biopsy.

MCC was first recognized as an entity in the 1970s, when its pathologic criteria were defined and its distinct clinical behavior was characterized (Toker, 1972). Early studies hypothesized that the lesion arose from Merkel cells in the epidermis, although recent observations suggest that pluripotent dermal stem cells are the origin (Becker, 2010; Huber, 2014). MCC presents most commonly in white males in their 7th or 8th decade of life. The primary etiologic factors include exposure to ultraviolet radiation and immunosuppression, including HIV, chronic lymphocytic leukemia, and solid organ transplantation. However, recent reports link the development of MMC to Merkel cell polyomavirus (MCV) (Feng et al., 2008). The viral stimulation of the cell cycle is believed to be the driving force of the oncogenetic potential in polyomaviruses. The tumor has a nonspecific appearance. Clinicians think most lesions are benign prior to biopsy. One of the most difficult tasks for dermatologists, usually the sentinel specialist, is to manage the clinical differential diagnosis. The most frequent manifestation of the disease is a persistent, asymptomatic, red or pink papule or nodule that rapidly increases in size over weeks to months on sun-damaged skin. Blue or red solitary nodules and acneiform and plaque-like lesions are other presentations (Fig. 1). Lack of tenderness is also an important feature. Ulceration is observed only in very advanced tumors. Rarely, the tumor may present as plaques or subcutaneous masses without epidermal change. Up to 50% of MCC cases develop on the head and neck, followed by the limbs and trunk. Localization on the oral and genital mucosa represents less than 10% of cases (Becker, 2010; Haerle et al., 2013).

MCC can be associated with squamous cell carcinoma in situ and invasive squamous cell carcinoma (Fig. 1) and less frequently with basal cell carcinoma, atypical fibroxanthoma, and follicular cyst (Mitteldorf et al., 2012; Jung et al., 2007). Clinically, differential diagnosis includes basal cell carcinoma, amelanotic melanoma, cutaneous lymphoma, adnexal tumors, squamous cell carcinoma, pyogenic granuloma, or cysts (Wong and Wang, 2010; Wang et al., 2011). An atypical vascular dermoscopic pattern with linear irregular vessels, milky pink areas, architectural disorder, and structureless areas are not specific but can aid early biopsy of the lesion (Dale et al., 2012; Jalilian et al., 2013). Differential diagnosis from salivary gland carcinoma may be almost impossible (Huber, 2014).

Several tumor characteristics that may lead a clinician to suspect MCC were included under the acronym "AEIOU" (A: asymptomatic/lack of tenderness; E: expanding rapidly; I: immune suppression; O: older than 50 years; U: UV-exposed/fair skin (Wong and Wang, 2010; Heath et al., 2008)). However, multiple non-MCC benign and malignant tumors may have at least 3 of these features (Zager et al., 2014).

In order to ensure early diagnosis, biopsy or excisional biopsy should be performed if the lesion has any suspicious features. The National Comprehensive Cancer Network Guidelines[1] (NCCN) indicate that the goal of excision is to obtain a histologically negative margin; the guildelines also recommend 1–2 cm margins down to the fascia when possible. Historically, wide local excision with surgical margins of 2–3 cm has been recommended (Zager et al., 2014; Bichakjian et al., 2007a). Moh's micrographic surgery permits tissue conservation and identification of tumors that require wide margins (Prieto et al., 2013; Huber, 2014).

Following meticulous work-up of the patient, some MCCs (10–20%) present as metastatic disease with no evidence of a primary tumor. The carcinoma of unknown primary is very difficult to manage clinically, although it has a better overall survival rate when compared with IIIB stage MCC (Huber, 2014; Tarantola et al., 2013).

3. Diagnostic imaging: radiologist and nuclear physician

The main roles of imaging in the evaluation of MCC concern staging, surgical and radiotherapy planning, treatment response assessment, and follow-up (Nguyen and McCullough, 2002; Tirumani et al., 2013). Due to the rarity of MCC, there are few reports on the imaging findings of this tumor and there is no universally accepted imaging algorithm for MCC (Nguyen and McCullough, 2002; Gollub et al., 1996; Eftekhari et al., 1996; Peloschek et al., 2010; Colgan et al., 2012). Morphological imaging methods, that is, ultrasonography (US), computed tomography (CT), and magnetic

[1] http://www.nccn.org/professionals/physician_gls/pdf/mcc.pdf.

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