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Overview

Merkel Cell Carcinoma: Current Management and Controversies

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Abstract

Merkel cell carcinoma is a rare skin tumour with a poor outcome and high rates of both local and distant recurrence despite radical management. We review the management of local and locoregional disease, and the role of sentinel lymph node biopsy in staging. This overview aims to highlight some of the controversies regarding the current treatment of this disease, which seems to be on the increase. Data are conflicting as to whether there is any survival benefit from adjuvant primary site or regional nodal irradiation, partly due to the lack of prospective clinical trials. We also review the evolving role of primary radiotherapy and suggest areas where ongoing research is urgently required.

Key words: Locoregional disease; Merkel cell carcinoma; radiotherapy; sentinel lymph node biopsy; staging; systemic therapy

Statement of Search Strategies Used and Sources of Information

This overview was written based on a search of the literature for radiotherapy in Merkel cell cancers. 'Merkel cell' and 'radiation/radiotherapy' were the primary search terms. The primary search was carried out via PubMed and other articles were sourced from related papers or those referenced in these articles.

Introduction

Merkel cell carcinoma (MCC) was first described in 1972 [1]. These rare tumours, often classified as neuroendocrine tumours of the skin, are rapidly growing, often occurring in the elderly, on sun-exposed regions [1].

The incidence of MCC, although low, is rising and is increasing more rapidly than other skin tumours, e.g. malignant melanoma. American SEER data have shown age-adjusted incidence rates trebled between 1986 and 2001, from 0.15 to 0.44 cases per 100 000 with a corresponding annual increase in incidence of 8% compared with 3% in melanoma [2]. Increasing incidence is perhaps attributed to a combination of longevity, increased reporting and improved screening/detection [2].

The management of MCC varies globally, with no clear consensus on adjuvant treatment with radiotherapy and chemotherapy. Much of the data regarding treatment are retrospective and extrapolated from small case series. Here we review the current management of MCC and highlight issues where urgent research is needed.

Aetiology

The aetiology of MCC is largely uncertain, although there is some evidence that immunosuppression is a factor, including HIV infection – with a relative risk of 13.4 times the general population [3]. Recently, the polyomavirus group has been linked with MCC. The MCC polyomavirus (MCPyV) has been isolated from MCC tissue and thought to be present in up to 80% of MCC [4]. The MCPyV viral genome seems to integrate into the cellular genomes of the tumours and is strongly implicated in driving the oncogenic activity of these cancers.

Ultraviolet radiation may be a cause, and corresponds with the sites of these tumours, often on sun-exposed skin, mostly (94%) in the White population [2]. Rates of MCC are

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significantly higher in psoriasis patients receiving Psoralen with Ultraviolet A treatment (PUVA), with a relative risk 100 times higher [5] than the general population.

Pathology

Histologically, MCCs are small round blue cell tumours and need to be distinguished from metastatic skin deposits from other neuroendocrine carcinomas, particularly small cell carcinoma of the bronchus (SCLC). Immunohistochemical analysis with the marker cytokeratin-20 is specific for MCC, yielding a positive stain in most cases (sensitivity 89–100%) [6]. Rarely (4.6%) SCLC may also stain positive for cytokeratin-20 and further analysis is needed [7]. Cytokeratin-7 is characteristically negative in MCC [6] and may be positive in SCLC, and further distinction can be ascertained with thyroid transcription factor, which is invariably negative in MCC but positive in SCLC (83–100% cases) [6]. Neurofilament protein is frequently found to be expressed (63–100%) on MCC tumours and consistently absent in SCLC [7]. Before the widespread use of cytokeratin markers in the 1990s, there may have been significant tumour misdiagnosis [8,9].

Clinical Features

MCC classically presents as a painless, violaceous lump on the skin, sometimes ulcerated or multifocal (Figure 1). The head and neck is the most common primary site (48%), followed by upper limb (19%), lower limb (16%) and trunk (11%) [10].

Most (73%) present with localised (stage I–II) disease, 23% have regional disease (stage III) and 4% have metastatic (stage IV) disease [11]. A small number (3.3%) may present as isolated metastases from an unknown primary [11]. For those with stage IV disease, common sites of metastases include distant lymph nodes (60%), distant skin (30%), lung (23%), central nervous system (18%) and bone (15%) [11].

Five year survival is 57% for localised disease, 39% for regional disease and 18% for metastatic disease [12,13].

Investigations and Staging

Imaging

There is no consensus on the role of imaging for localised MCC. If a patient has symptoms suggestive of metastases, it would be sensible to investigate with appropriate imaging techniques, e.g. computed tomography or magnetic resonance imaging, depending on site. For patients with high-risk disease (tumour >2 cm and/or clinically node positive) it may be prudent to exclude disseminated disease by computed tomography staging. Computed tomography-based imaging in the detection of distant disease does, however, carry a potentially high false-positive rate (52%), risking suboptimal treatment of true localised disease [8].

FDG-positron emission tomography scanning has been suggested as a more accurate staging modality, and one small study has shown a change in staging in one-third of patients and management in 43% [14]. A recent meta-analysis of the role of positron emission tomography-computed tomography showed both high sensitivity (90%) and specificity (98%), suggesting a potential role in routine staging [15].

The Role of Sentinel Lymph Node Biopsy (SLNB)

Accurate staging of MCC tumours, particularly lymph node status, is vital in determining the best treatment for each individual. MCCs have a much higher incidence of nodal metastases than other skin tumours, e.g. melanoma. Of 6764 patients in the National Cancer Database, 1836 patients (27%) had nodal disease at presentation and 7% had distant disease [13].

Even those with clinically node-negative disease have a high incidence of nodal metastases at surgery [8]. Of 122 patients, SLNB was positive in one-third (32%) of patients who were clinically node-negative [8], in keeping with other reports [16]. Here, the risk of relapse (site unspecified) in SLNB-positive disease was three times higher (60%) than in SLNB-negative disease (20%, $P = 0.03$). Furthermore, SLNB-positive patients who received

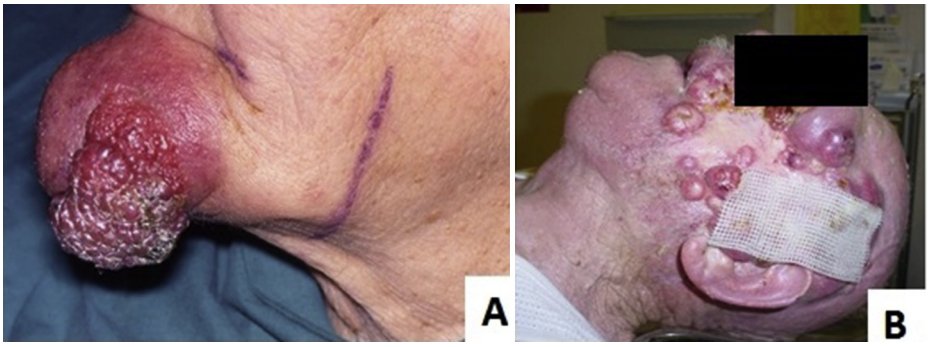

Fig 1. Merkel cell carcinoma presenting as a localised lesion on the chin (A) and widespread locoregional disease on the face (B) (Courtesy: Dr K. Fife, Cambridge).

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