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Single-centre experience of primary cutaneous Merkel cell carcinoma of the head and neck between 1996 and 2014

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Abstract

We retrospectively reviewed the management at our centre of 25 patients with Merkel cell carcinoma (MCC) of the head and neck. We obtained details of the operation, including wide local excision, sentinel lymph node biopsy (SNB), neck dissection, postoperative radiotherapy, and clinical outcomes, from patients' records. All patients were white, 11 were men and 14 women, mean age at presentation 81 years (range 67-90). At the time of diagnosis, 18 patients had stage I disease, and 7 stage II disease. Twenty had wide local excision and radiotherapy, and 5 had wide local excision alone. Wide local excision and radiotherapy are successful treatments. In patients with no sign of metastases, SNB at the time of excision is a well-researched option and should be considered the gold standard of care.

Keywords: Merkel cell carcinoma; Head and neck Merkel cell carcinoma; Sentinel node biopsy

Introduction

Over 100 articles on Merkel cell carcinoma (MCC) were published worldwide in the first half of 2014. Most reported data originates in the United States (US) and Australia, and organisations such as the US Surveillance, Epidemiology, and End Results (SEER) programme allow access to a large number of cases for analysis.

To our knowledge, the study by Blythe et al. in 2014 is the largest single-centre case series of MCC of the head and neck in Europe.[1] The incidence of MCC tripled between1986 and 2001, and quadrupled up to 2006, and the annual incidence in the US is 0.6/100 000.[2] About 46% - 48% of lesions affect the head and neck, 35% - 38% the extremities, and 11% - 17% the trunk.[3]

Merkel cells, which are found in the skin and some parts of the mucosa of all vertebrates, were discovered in1875 by Friedrich Sigmund Merkel. Various possible functions have been proposed for them, including somatosensation, endocrine function, and chemosensation. Initially they were thought to originate from neural crest cells, but recent investigations have confirmed an epidermal derivation.

The pathogenesis of MCC is not fully understood. The Merkel cell polyomavirus (MCPyV), which is a normal finding in human skin, is thought to promote tumorigenesis in MCC, and has been found in 80% of samples of the disease.[4] Monoclonal integration in the host genome suggests that viral infection precedes clonal expansion of the tumour.[4] However, the fact that tumours with and without the virus have different prognoses, different oncogenic expression, and a different histological appearance, suggests that they have different aetiologies, and the mechanism of viral infection alone is not likely to explain its pathogenesis. It is not currently known whether MCPyV infection may also have a causative role in other diseases.[5]

The role of ultraviolet radiation (UV-B) in the oncogenesis of MCC is well documented,[3] and a typical ultraviolet B–induced p53 mutation has been reported in a MCC cell line.[6] A 100-fold increase in the incidence of tumours has been reported in patients treated with methoxsalen

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Table 1
Important features of Merkel cell carcinoma.[7]

Acronym	Meaning
A	Asymptomatic/lack of tenderness
E	Expanding rapidly
I	Immunosuppression
O	Over 50 years of age
U	Site exposed to ultraviolet light on a person with fair skin

and ultraviolet-A for psoriasis, and exposure to arsenic and damage by infrared radiation have been implicated as possible factors in its development. Its incidence is considerably increased in immunocompromised patients, particularly those with suppression of T-cell immunity. There is also a raised risk in patients with chronic lymphocytic leukaemia (30-fold),[7] acquired immunodeficiency syndrome infection (13-fold), and recipients of organ transplants (10-fold).

MCC is confirmed histopathologically, and has been classified into three distinct subtypes: trabecular, intermediate, and small cell. Routine haematoxylin and eosin staining shows small, round, blue cells with large prominent nuclei. Further immunohistochemical analysis is required for accurate delineation. Cytokeratin-20 (CK-20) is the most sensitive (87.4%) and stains in a characteristic dot-like pattern, but cutaneous metastases of small-cell lung cancer also stain for CK-20 in up to 4.6% of cases. Thyroid transcription factor 1, which is expressed in small-cell lung cancer but not in MCC, allows these diseases to be distinguished.[8] Heath et al. showed that important features of MCC can be summarised by the acronym: AEIOU (Table 1).[7] In their series, 89% of cases showed 3 or more of them.

MCC usually presents as a non-tender, rapidly growing, painless, single, red to violet, firm, intradermal papule or nodule.[9] Epidermis overlying the tumour is usually preserved, but ulceration or crusting can occur in those that present late. Early tumours can appear deceptively benign and have been mistaken for basal or squamous cell carcinoma, amelanotic melanoma, keratoacanthoma, adnexal tumours, or cutaneous metastatic disease. Clinical staging guidelines were published in 2010 by the American Joint Committee on Cancer (AJCC) (Table 2).

We know of 5 different staging systems that are in active use. The most recent, which was based on an analysis of prognostic factors in 5823 patients with the disease in the US, uses information from the National Cancer Data Base, and is echoed in the current treatment guidelines from the National Comprehensive Cancer Network (NCCN).[10]

Imaging guidelines vary and include ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and octreotide scans.[11] MCC is a 2-deoxy-2-[fluorine-18]fluoro- D-glucose (FDG) avid tumour, and FDG-positron emission CT (PET-CT) has a sensitivity of 92% and specificity of 100% for metastatic disease.[12] This type of imaging is increasingly available and should be considered the gold standard.

Around one-third (29% - 32%) of patients with no clinical sign of metastases at presentation, have microscopic disease in the lymph nodes.[13,14] This high propensity to metastasise was reported by Schwartz et al. who found that almost 60% of patients had regional or distant metastases at presentation.[15] Sentinel lymph node biopsy (SNB) seems to reliably stage clinically unaffected regional nodes and to identify lymphatic pathways. A negative result seems associated with a good prognosis, but it has been suggested that the status of the sentinel nodes is not predictive of survival in MCC of the head and neck.[16]

The risk of local recurrence or systemic metastatic disease in patients with a positive sentinel node biopsy remains high and warrants consideration of aggressive adjuvant therapy.[14] Analysis of data from the Surveillance, Epidemiology, and End Results Program (SEER) database by the AJCC showed that the absence of microscopic evaluation of regional nodes in stage I and II disease is, in itself, a poor predictive factor.

We have retrospectively reviewed the management and outcomes of patients diagnosed with cutaneous MCC of the head and neck.

Method

We identified patients treated at the Royal Surrey County Hospital in Guildford, Surrey, between 1996 and 2014 from 4 separate databases. They all had histopathologically confirmed primary cutaneous MCC of the head and neck and were staged retrospectively using the AJCC 2010 staging system.

Variables included age at diagnosis, sex, site and stage of tumour, nodal management, treatment, adjuvant therapy, recurrence, and survival.

Table 2
Clinical staging guidelines for Merkel cell carcinoma by the American Joint Committee on Cancer (AJCC) 2010.

Stage	Local disease	Lymph nodes	Metastasis	5-year disease-free survival
I (T1)	Yes	No	No	79% with –ve SNB 60% with no SNB
II (T 2, 3, 4)	Yes	No	No	58%, 49%, 47%
III (N+, any T)	No	Yes	No	Micro 42% Macro 26%
IV (Any T or N)	No	Yes	Yes	18%