Merkel Cell Carcinoma – Rare and Often Underestimated

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Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine carcinoma arising in the dermo-epidermal junction. In the UK an estimated 1,515 cases of MCC were diagnosed between 1999-2008, equating to a two-fold increase in incidence over this period (source: National Cancer Intelligence Network). Despite general improvements in diagnosis and management of skin cancer, the prognosis from MCC's remains poor with 79% of patients with MCC succumbing to the disease within two-years of diagnosis, a mortality rate double that of malignant melanoma [1].

The major barrier to effective management of MCC is its rarity and thus the paucity of available data in the literature. To date there is no published UK guidance as to the recommended management paradigm for MCC. The poor prognosis related to MCC is undoubtedly due to its aggressive biological behaviour. However this is likely compounded by delays in diagnosis. In reality, few physicians would see this type of rare cancer in their lifetime. This article serves to review some of the general features as well as the best available data for the current and future management of this rare but lethal skin cancer.

Pathophysiology of MCC – a historical perspective

In 1875 Freidrich Merkel first described mechano-receptors that are widely found in the basal layer of edpidermis, hair follicles, sweat glands and some mucosal sites. They form a complex system of cutaneous neural network and are the prominent apparatus for detecting pressure and vibration through the skin. These cells unlike other cellular components of the skin show both neuroendocrine as well epithelial differentiation.

The first known description of a skin cancer with neurosecretory type cells was made in a series of five patients described by Cyril Toker in 1972 [2]. It was initially considered as variant of sweat gland carcinoma and called 'trabecular carcinoma'. However, it was not until 1980 when De Woolf-Peters' described these as neuroendocrine skin cancers and coined the term 'Merkel Cell Carcinoma'.

While both Merkel cells and MCC share similar structural and immunohistochemical profiles, there are fundamental differences in their anatomical distribution and expression of neurosecretory proteins. Therefore despite early suggestions, it is as yet unclear whether MCC truly arises from Merkel cells.

Clinical Features

MCC usually appears as a firm, painless lesion, found on sun-exposed areas. They are typically red, blue or skin coloured, vary greatly in size and may rarely ulcerate (Figure 1). The risk factors for developing MCC include; Age > 65 years, fair skin, sun exposure and Immuno suppression (e.g. HIV, chronic lymphocytic leukaemia, organ transplantation).

Advanced disease at diagnosis is a poor prognostic factor, making early detection essential. A study by Heath et al. of 195 proven cases of MCC showed 88% were asymptomatic and over 56% were presumed benign at biopsy (differential diagnoses included dermatofibroma, lipoma or cysts) [3]. The group also identified five clinical characteristics (summarised as the acronym "AEIOU" – Table 1) that were shared amongst their cohort, with 89% possessing three or more features.

Table 1: AEIOU features of MCC

A	Asymptomatic (painless)
E	Expanding rapidly (<3 months)
I	Immunosuppressed
O	Older than 50 years
U	UV exposed site (location)

Histological diagnosis

Histology is the gold standard in diagnosing MCC. They may be classified according to their growth pattern (diffuse, trabecullar or infiltrative) or cell size (small, intermediate or large cell). The principal mode of histological diagnosis is by using a panel of immunohistochemical markers of epithelial differential, commonly CK 20, as well as neuroendocrine markers such as synptophysin, Chromogranin A, Somatostatin, CD-56 and Neuron Specific Enolase (NSE). The presence of perinuclear dot pattern of cytokeratin is considered pathognomonic.

Staging

As compared with melanoma, lymph node metastases in MCC are more common and can occur in 10--30% of cases at presentation [4]. Lymph node status is the single most important prognostic indicator in MCC and thus Sentinel Node biopsy (SLNB) plays a significant role in assessing loco-regional nodal basins in clinically node negative disease. A study by Allen et al found a significant difference in five-year disease-specific survival between clinically node-negative (75% survival) and those confirmed pathologically as negative (Survival 75% vs 97% respectively, $p = 0.009$) [4]. Gupta et al also found the three-year recurrence rates to be three times higher in patients with a positive SLNB (60%) as compared to those with a negative biopsy (recurrence rates of 60% vs 20% respectively, $p = 0.03$) [5]. To date, no one imaging modality has been proven to be superior in detecting nodal disease pre-operatively. However, in the presence of clinically malignant regional lymph nodes, use of CT and/or FDG-PET/CT is advo-

Table 2: Adverse histological features

Mitotic count >10/ mm2
Small cell subtype
Lymphovascular invasion
CD44 expression
Tumour infiltrating lymphocytes (TILs)
Necrosis

cated for assessing the presence of systemic spread.

To date several adverse histological features have been described (Table 2) but they have generally yielded inconsistent results. More recently, Lemos and colleagues have again shown SLN status to improve prognostic accuracy but also suggested that for patient with isolated local disease, small < 2cm lesions were associated with better survival [6].

Management

Upon clinical suspicion, a diagnostic biopsy is mandatory for confirming the diagnosis of MCC. Clinical assessment should also include regional nodal basins, augmented with sonographic and tissue analysis (FNA or core biopsy) of clinically abnormal lymph nodes. The definitive treatment of the primary lesion is excision (1-2cm margins depending on anatomical site) with the ultimate goal of achieving a clear microscopic margin. It is recommended that any reconstruction of the local defect is carried out once histological margins are deemed secure. If a skin graft is required, a split skin graft is preferred which allows better surveillance for local recurrence.

Although in practice a 1-2cm (macroscopic) margin is aimed for, the disorganised and infiltrative growth pattern of MCC makes recommending an ideal margin difficult. Meeuwissen and colleagues from Australia showed that a simple excision with 0.5cm margins resulted in 100% recurrence (n = 38) [7]. O'connor et al have also showed that wider excisions of > 2.5cm may still be associated with up to 49% locoregional recurrence or persistence of disease [8]. Boyer et al achieved a lower recurrence rate of 16% using Mohs micrographic surgery and a surgical margin of 1cm (n = 25), but it is noteworthy that in their small series, addition of radiotherapy reduced their three-year recurrence rates to 0% [9]. A meta-analysis by Lewis et al (2006) has subsequently showed adjuvant radiotherapy to result in 3.7 fold decrease in five-year local recurrence rates and 2.9 fold decrease in regional recurrence rates if regional nodal basins were also included [10]. It is however suggested that for a fully excised small (< 1cm) lesions and in the absence of unfavourable histological features (see Table 2), radiotherapy is unlikely to be beneficial.

In clinically node negative disease, SLNB is indicated although the variability in head and neck lymphatic anatomy can be challenging. The management of clinically node positive disease is with regional lymphadenectomy and in certain circumstances radiotherapy, but not both. Management of microscopic nodal disease is controversial particularly as comparable locoregional control rates are seen between lymphadenectomy and radiotherapy monotherapy. Results from larger studies with longer follow-up time are awaited [11].

Chemotherapy to date has not been shown to alter outcomes and its use is limited to the palliative setting.

The Future

The discovery of the "Merkel cell polyomavirus" (MCPyV) in 2008 has generated considerable interest both in terms of its potential therapeutic and prognosticating applications. MCPyV DNA has been found to be clonally integrated in 80% of MCC as compared to 10% of melanomas and other skin cancers [12]. While this finding may suggest a direct oncogenic role for MCPyV, the prevalence of exposure to polyoma viruses and the relative low incidence of MCC highlights many unanswered questions. Evidence to support the link between MCC and MCPyV is the persistent expression of the virally derived T-antigen [13]. *In vitro*, cell lines derived from MCPyV positive MCC tumours remain dependant on expression of the MCPyV T-antigens for maintaining their transformed phenotype.

Where MCPyV may play a role is in defining a subclass of the disease with better prognosis. Touze et al have shown that patients with high levels of serum antibodies against the VP1 major capsid protein of MCPyV have better outcomes [13]. Paulson and colleagues have also showed that peri- and intra-tumoral infiltration with MCPyV specific CD8+ T-cells may be associated with a better prognosis. Such findings have raised the possibility of targeted immunotherapy with T-cells [14]. The stumbling block for this however, is the variability of HLA-1 expression in MCC with approximately 50% showing reduced or loss of MHC expression. There are suggestions that this may be reversed where in MCC cell lines, Iterferon-B seems to upregulate Class-I HLA expression. In Japan, a single case of locally recurrent MCC has been successfully treated with intra-tumoral Interferon-B injections [15].

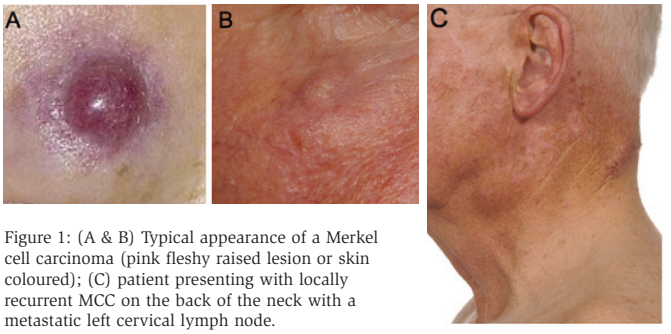

Figure 1: (A & B) Typical appearance of a Merkel cell carcinoma (pink fleshy raised lesion or skin coloured); (C) patient presenting with locally recurrent MCC on the back of the neck with a metastatic left cervical lymph node.

Conclusion

Merkel Cell Carcinoma is a rare neuroendocrine skin cancer with a high disease-associated mortality and a fast rising incidence. Its effective management requires a high index of suspicion with early diagnosis and a multidisciplinary treatment approach. The discovery of the Merkel Cell Polyoma virus has been an important development that may pave the way towards alternatives in prognostication as well as targeted immunotherapy in the future. ■

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