Look out for AEIOU

DERMATOLOGY

Although rare, GPs need to be aware of Merkel cell carcinoma, the most malignant of all skin cancers.

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MERKEL cell carcinoma is the most malignant of all skin cancers, with more than one-third of patients dying of the disease. It is a rare malignancy, which predominantly affects sun-exposed areas in elderly patients.

Background

Merkel cell carcinoma of the skin is a rare neuroendocrine malignancy that exhibits an aggressive clinical course and possesses unique clinicopathological features.

Management is often complex and requires multidisciplinary input. Whereas the inherent dangers of melanoma are well known to the public, Merkel cell carcinoma remains unfamiliar, despite the fact that one-third of patients will die of the disease within five years of diagnosis.[1]

Merkel cell carcinoma makes up a tiny proportion of all skin cancers and it is important for GPs to be aware of this condition so that appropriate management is initiated.

Incidence

The incidence in Queensland is 1.6 per 100,000, which is higher than in other states due to the high ultraviolet levels in Queensland.

Men (2.5 per 100,000) have a higher incidence than women (0.9 per 100,000), and rates peak at 20.7 per 100,000 for persons 80 years or older.

The overall incidence of Merkel cell carcinoma has been increasing at a rate of 2.6% per year from 1993 onwards.[2]

The reasons for this are speculative, but may in part be due to increased awareness of the diagnosis, patients living longer and the increased prevalence of immunosuppression in the community.

The acronym AEIOU — Asymptomatic, Expanding rapidly, Immunosuppression, Older than 50, and UV exposure — summarises the characteristic features of this disease.

Aetiology

UV light has been implicated in the aetiology as there is an increased incidence related the UVB index, and Merkel cell carcinoma occurs predominantly in sun-exposed areas of the skin.

A Merkel cell virus (MCV) has also been implicated by detecting the viral genome in 80% of Merkel cell carcinomas.[3] In Australia, the proportion with viral-related Merkel cell carcinoma is approximately 20% and the majority appear to be related to UV.

Clinical aspects

The lesions usually arise on areas of sun exposure, with 50% occurring on the head and neck region and 40% on the extremities.

Caucasian males predominate, and the median age is 70, with about 10% associated with immunosuppression.

Most lesions are asymptomatic and characterised by a pattern of rapid growth. The lesions have a characteristic red or pink colour. The acronym AEIOU — Asymptomatic, Expanding rapidly, Immunosuppression, Older than 50, UV exposure — summarises the characteristic features of this disease.[4]

Despite its distinct clinical characteristics, the diagnosis is rarely made clinically, and only becomes apparent at biopsy.

The presence of these features should alert the GP to the potential diagnosis, and biopsy should proceed as soon as practicable. These clinical features are illustrated in the image.

Examination should be carried out with good light and magnification, looking for satellite lesions. The draining lymph nodes should be carefully evaluated as they are commonly involved.

There is commonly coexistence of other skin cancers or evidence of solar damage.

Patterns of spread

Examination of 5823 cases of Merkel cell carcinoma from the National Cancer Database showed that 66% presented with local disease, 27% presented with nodal disease and 7% with distant disease.[5]

Locally, this disease spreads via the dermal lymphatics and then to regional nodes. The presence of involved nodes increases the risk of distant metastases.

Investigations

The histological diagnosis is most commonly made by excision biopsy of the primary lesion.

For larger lesions, a punch biopsy should be performed prior to definitive treatment.

Merkel cell carcinoma

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is comprised of small blue cells, which may be confused with basal cell carcinoma, lymphoma, small cell carcinoma or neuroblastoma. Immunoperoxidase stains secure the diagnosis, and typically will be positive for neuroendocrine and cytokeratin markers. If there are palpable nodes, a fine needle aspirate should be done to confirm positivity.

All patients with Merkel cell carcinoma require clinical and radiological staging so that treatment can be tailored to the extent of the disease. CT imaging of the relevant nodes should be undertaken, and the lungs and liver examined.

The use of PET imaging is being explored in this disease, but currently remains unfunded in Australia.

Stages I and II Merkel cell carcinomas are defined as disease that is localised to the skin at the primary site. Stage I is for primary lesions less than or equal to 2cm, and stage II is for primary lesions greater than 2cm. Stage III is defined as disease that involves regional lymph nodes. Stage IV disease is found beyond regional lymph nodes.

Overview of treatment

Treatment is aimed at cure if the disease is confined to the primary site and nodes (stages I-III).

Factors that need to be taken into account are the patient's age and general condition, the site/stage of the disease, as well as preference for treatment.

The factors affecting treatment are summarised in the table opposite.

The mainstays of treatment are surgery and radiotherapy. Unlike melanoma of the skin, Merkel cell carcinoma is a very radiosensitive disease and radiotherapy can be used as definitive treatment or as an adjuvant treatment following surgery.

The primary site, as well as the draining nodes, should be treated because of the high incidence of nodal spread.

Most Merkel cell carcinomas (stages I-II) are amenable to surgical excision and this allows the diagnosis to be made.

If there are satellite lesions, or if surgery will have an adverse impact on cosmesis or function, radiation may be used as the definitive treatment.

Surgical margins do not need to be wide if adjuvant radiotherapy is to be given, as local control appears to be equivalent for margin positive and margin negative disease with the appropriate use of radiotherapy.[6]

Adjuvant radiotherapy courses usually extend over a five-week period, and offer high levels of regional control.

For stage I Merkel cell carcinoma, the use of adjuvant nodal radiotherapy has been shown in a randomised trial to reduce the risk of regional relapse from 16.7% to 0%, and this has now become the standard of care in clinically node-negative patients.[7]

The side effects of radiotherapy will depend on the site to be treated. Patients will experience a skin reaction with dry or moist desquamation as well as fatigue.

Radiation mucositis, xerostomia and loss of taste may occur with radiotherapy in the head and neck site.

With the availability of three-dimensional planning and intensity-modulated radiation therapy, radiation oncologists are able to minimise dose to normal tissues and reduce the side effects of treatment.

Although early Merkel cell carcinoma may be managed with wide surgical excision alone in carefully selected patients, there is compelling evidence that the addition of radiotherapy improves loco-regional control and survival.[8]

Radiotherapy is not necessary for lesions less than 1cm in size, with no lymphovascular invasion, that have been widely excised with clear margins and a negative sentinel node biopsy, and not associated with any immunosuppression.

With the increasing use of sentinel node biopsy, which provides prognostic information, adjuvant radiotherapy may be avoided if the biopsy result is negative, accepting that the patient may progress in 20% of cases.[9]

However, all patients with a positive sentinel node biopsy result require nodal treatment with surgery or radiotherapy.

Like small cell lung cancer, Merkel cell carcinoma is a chemosensitive disease. Chemotherapy has been mainly used as a palliative treatment in patients with stage IV disease.

The use of adjuvant chemotherapy and chemoradiotherapy has been explored in high-risk Merkel cell carcinoma in an attempt to reduce the risk of distant spread and improve survival.[10]

However, at present, the routine use of chemotherapy is not recommended outside the context of a clinical trial.

New systemic options are being evaluated, which may impact management. Blockade of programmed death, an inhibitory receptor expressed by T-cells, can overcome immune resistance. This is being explored in patients with recurrent and metastatic Merkel cell carcinoma and shows promise.[11,12]

There are no randomised trials comparing the different treatment strategies, and a multitude of surgical and non-surgical approaches exist.

A multidisciplinary approach is favoured to help achieve good treatment outcomes while minimising the toxicities of treatment.[13]

Prognosis

The overall survival for Merkel cell carcinoma in Queensland in a population-based study was 41% at five years.[2]

This makes Merkel cell carcinoma the most malignant of skin conditions.

Results are better for patients younger than 70, for head and neck sites, and for earlier stage disease.

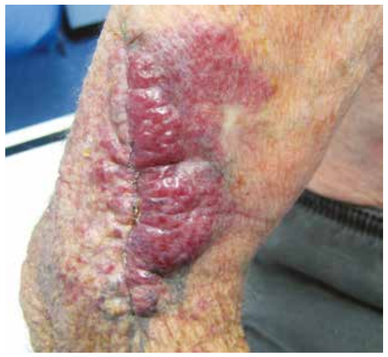
Implications for GPs

Although rare, GPs need to be aware of this very aggressive skin cancer, which needs urgent referral for ongoing specialist management.

Radiotherapy has been shown to increase survival and loco-regional control.

FACTORS AFFECTING TREATMENT FOR MERKEL CELL CARCINOMA

Patient factors	Tumour factors	Treatment factors
• Age and general condition • Renal and marrow function • Immunosuppression • Condition of the skin • Adjacent critical normal tissues • Patient preference	• T stage • N stage • Presence of distant disease • Site of the tumour • Molecular factors	• Availability of radiotherapy • Adequacy of the excision margins • Previous treatment with radiation



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