PRIMEVIEW

MERKEL CELL CARCINOMA

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Merkel cell carcinoma (MCC) is a rare neuroendocrine cutaneous tumour with high metastatic potential and mortality. MCC carcinogenesis can be initiated by DNA damage caused by chronic ultraviolet light (UV) exposure or by Merkel cell polyomavirus (MCPyV) infection.

DIAGNOSIS

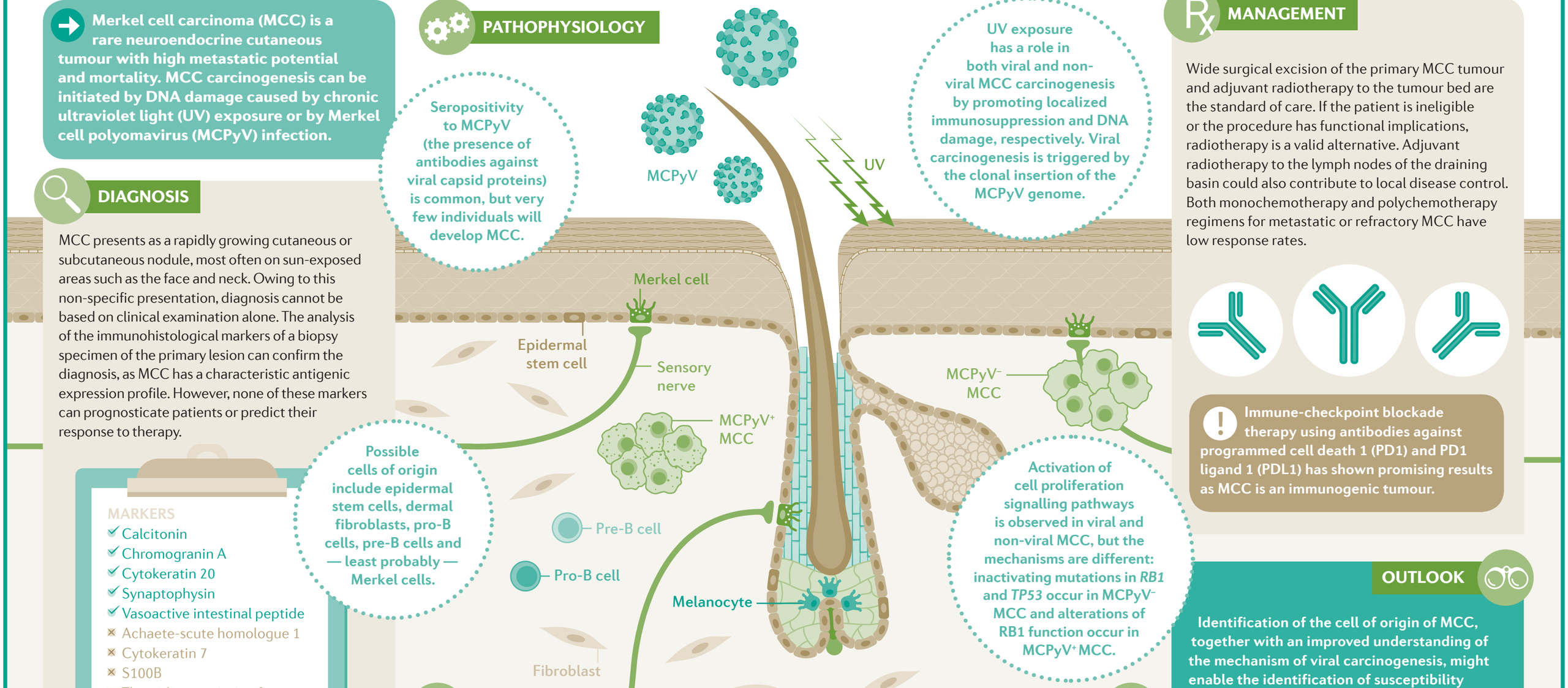
MCC presents as a rapidly growing cutaneous or subcutaneous nodule, most often on sun-exposed areas such as the face and neck. Owing to this non-specific presentation, diagnosis cannot be based on clinical examination alone. The analysis of the immunohistological markers of a biopsy specimen of the primary lesion can confirm the diagnosis, as MCC has a characteristic antigenic expression profile. However, none of these markers can prognosticate patients or predict their response to therapy.

MARKERS
- ✓ Calcitonin
- ✓ Chromogranin A
- ✓ Cytokeratin 20
- ✓ Synaptophysin
- ✓ Vasoactive intestinal peptide
- × Achaete-scute homologue 1
- × Cytokeratin 7
- × S100B
- × Thyroid transcription factor 1
- × Vimentin

MCC usually spreads to the lymph nodes first: sentinel lymph node biopsy should be considered even if the draining lymph nodes are not enlarged, as clinically occult metastases occur in ~30% of patients.

PATHOPHYSIOLOGY

Seropositivity to MCPyV (the presence of antibodies against viral capsid proteins) is common, but very few individuals will develop MCC.



UV exposure has a role in both viral and non-viral MCC carcinogenesis by promoting localized immunosuppression and DNA damage, respectively. Viral carcinogenesis is triggered by the clonal insertion of the MCPyV genome.

Possible cells of origin include epidermal stem cells, dermal fibroblasts, pro-B cells, pre-B cells and — least probably — Merkel cells.

Activation of cell proliferation signalling pathways is observed in viral and non-viral MCC, but the mechanisms are different: inactivating mutations in *RB1* and *TP53* occur in MCPyV⁻ MCC and alterations of RB1 function occur in MCPyV⁺ MCC.

PREVENTION

Because MCC incidence is very low, screening programmes are not available. Nevertheless, the biopsy of MCC-like lesions should not be delayed in high-risk individuals, such as elderly or immunosuppressed individuals and patients with a history of other skin cancers.

EPIDEMIOLOGY

Reported incidence of MCC is in the range of 0.3–1.6 per 100,000 individuals per year, and the median age at diagnosis is 75–80 years. In the Northern hemisphere, MCPyV⁺ MCCs account for the majority of cases; by contrast, in areas with high UV exposure, MCPyV⁻ MCCs are most prevalent.

MANAGEMENT

Wide surgical excision of the primary MCC tumour and adjuvant radiotherapy to the tumour bed are the standard of care. If the patient is ineligible or the procedure has functional implications, radiotherapy is a valid alternative. Adjuvant radiotherapy to the lymph nodes of the draining basin could also contribute to local disease control. Both monochemotherapy and polychemotherapy regimens for metastatic or refractory MCC have low response rates.

Immune-checkpoint blockade therapy using antibodies against programmed cell death 1 (PD1) and PD1 ligand 1 (PDL1) has shown promising results as MCC is an immunogenic tumour.

OUTLOOK

Identification of the cell of origin of MCC, together with an improved understanding of the mechanism of viral carcinogenesis, might enable the identification of susceptibility factors for MCPyV-driven carcinogenesis. Immune-checkpoint blockade therapy could greatly benefit patients with advanced-stage MCC. However, only around half of these patients respond to this treatment and a substantial number develop secondary resistance. Thus, an understanding of the mechanisms of primary and secondary immune escape is necessary to overcome these issues.

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