Merkel Cell Carcinoma: A Case Report and Brief Review of the Literature

ABSTRACT

Abstract: Merkel cell carcinoma (MCC) is a rare and aggressive cutaneous malignancy. It is seen most frequently in those over 60 years old and in Caucasian males. It usually presents as an asymptomatic rapidly growing violatious nodule on a sun exposed area. The mainstay of treatment is surgical by standard wide local excision or MOHs chemosurgery. Radiation is added frequently for local control. The only factor significantly associated with overall survival is the stage of disease at presentation. This stresses the importance of early diagnosis and treatment.

KEYWORDS: Merkel cell carcinoma, wide local excision, MOHs chemosurgery, adjuvant radiotherapy, review, case

Introduction

Merkel cell carcinoma (MCC) is a rare and aggressive cutaneous malignancy. Its cell of origin, the Merkel cell (MC), was first described in 1875 by Freidrich Merkel.[1]

Merkel cells are neuroendocrine cutaneous cells, which are not numerous and concentrated in touch sensitive areas, and in glaborous and hairy skin.[1] They are located within an intense epidermal sensory network in close association with slowly adapting type 1 mechanoreceptors which are known as MC-neurite complexes or Merkel discs.[1]

Cyril Toker described five cases of "trabecular carcinomas of the skin" in 1972[2] that was named MCC in 1980 following ultrastructural studies.[3] There are two hypotheses postulating the MC origin and subsequently that of MCC. The MC is thought to either differentiate from epidermal keratinocyte-like cells or, as with melanocytes, from stem cells of neural crest origin that migrated during embryogenesis.[1]

These theories have led to many names being proposed including: neuroendocrine cancer of the skin, small cell carcinoma of the skin and anaplastic cancer of the skin.[4]

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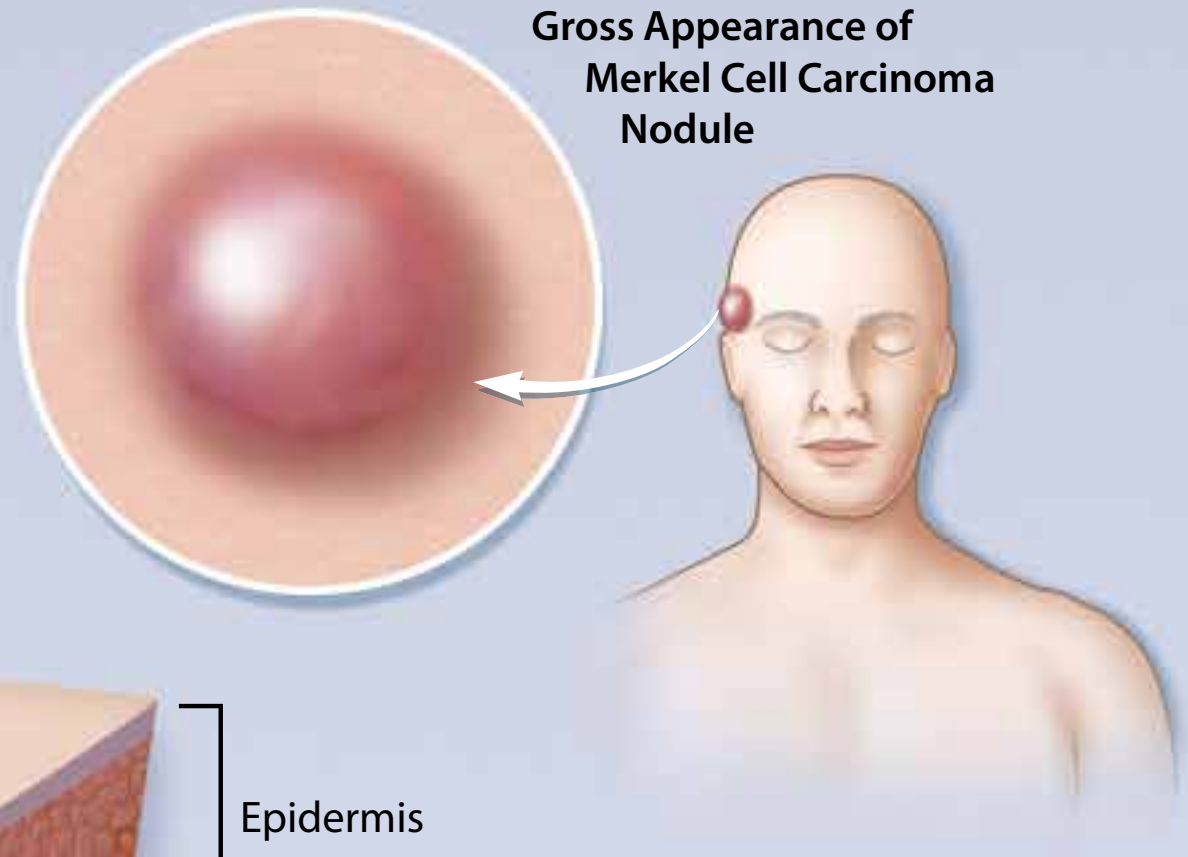
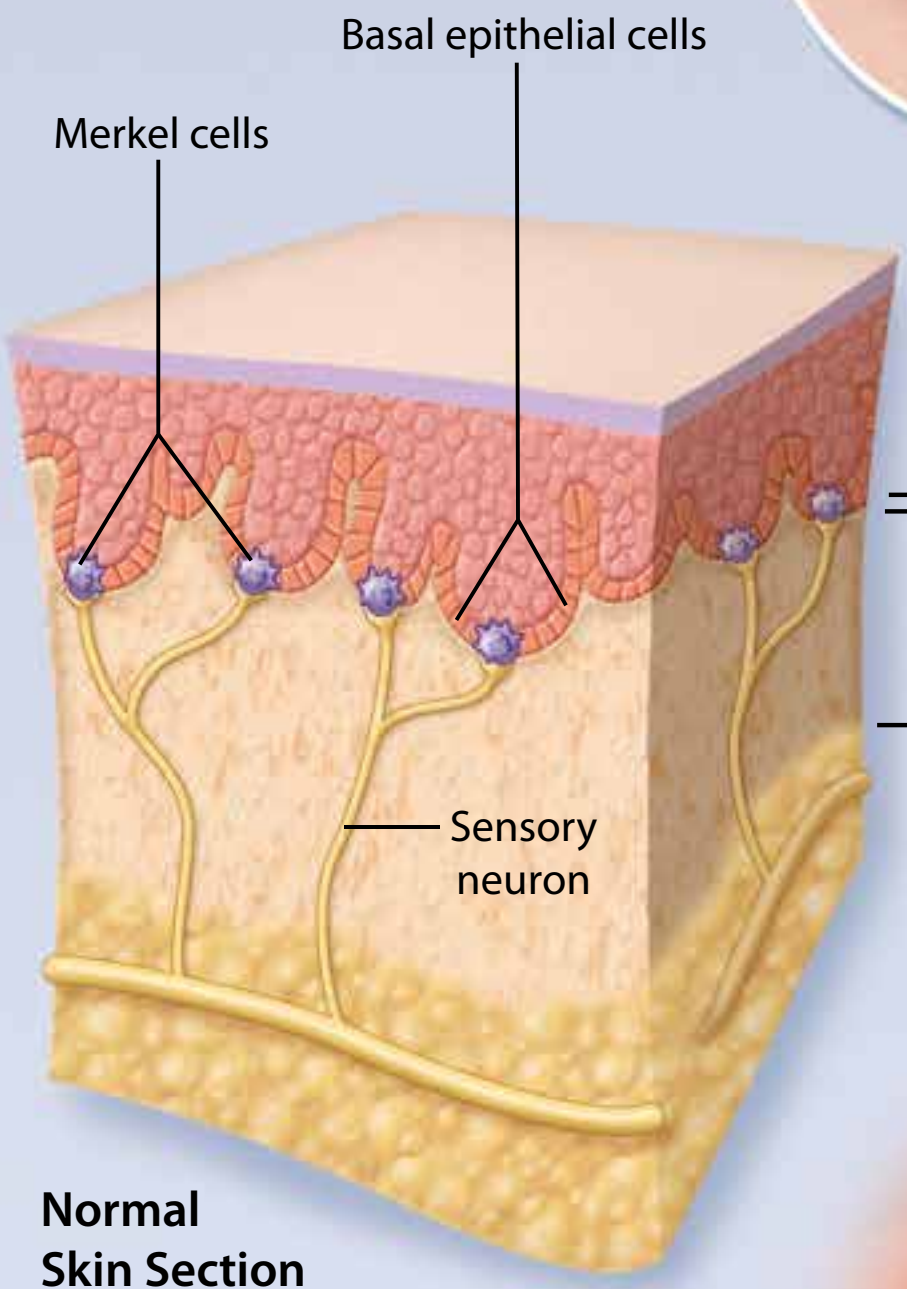
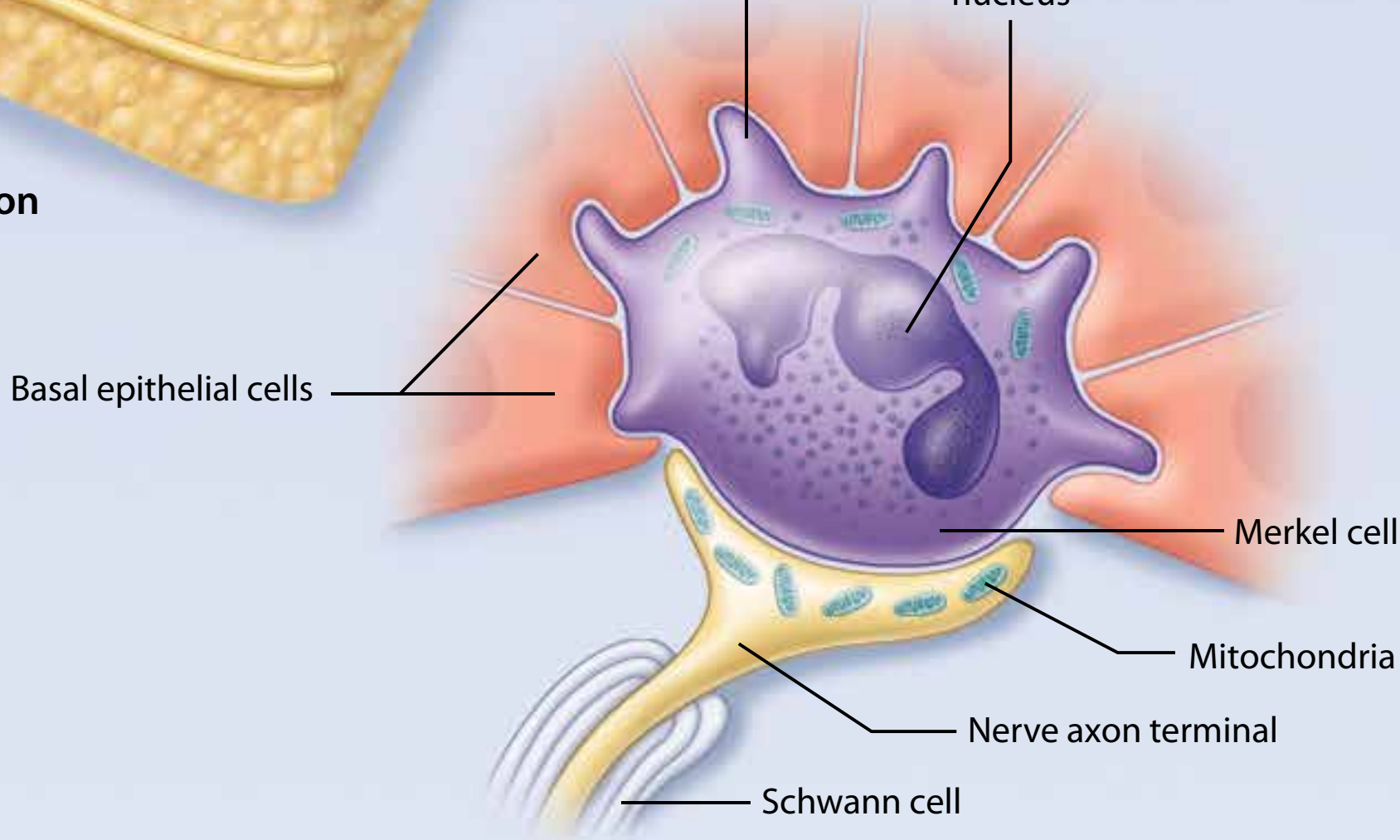
Merkel Cell Carcinoma

Gross Appearance of Merkel Cell Carcinoma Nodule





Normal Skin Section



A recently recognized oncogenic virus—Merkel cell polyomavirus (MCV)—may be a contributing factor in the pathogenesis of MCC.[5]

OVERALL, MCC IS MORE COMMON IN WHITES THAN BLACKS, IN THOSE OF ADVANCED AGE, AND IN MEN THAN WOMEN.

Incidence

MCC is a rare skin malignancy with incidence calculations based on United Sates (US) Surveillance, Epidemiology, and End Results (SEER) database report incidence of 0.23 per 100,000 for Caucasians,[6] a number similar to an estimate using the defined patient population of the Mayo Clinic;[7] about 470 new cases are diagnosed annually in the US.[8]

Overall MCC is more common in whites (94%) than blacks (1%), in those of advanced age (average 72 years), and in men than women (1.6-2.3:1). Men are also younger at diagnosis (71 years) compared to women (76 years).[9] Hodgson suggests that the MCC incidence rates have increased threefold over the 1986-2001 period.[10]

Case presentation

A 75 year-old Caucasian male patient was referred to our hospital from his primary care physician for management of a rapidly growing mass on the right temple. Past medical and surgical history was noncontributory. Physical exam revealed a tumour; a large, violacious, solid, firm mass measuring 4 cm in diameter and 3 cm in height. The differential diagnosis included Malignant Melanoma, and Kaposi's sarcoma and other non melanoma skin cancers.

The patient underwent complete and wide local excision of the tumour with 2 cm margins radially and periosteum on the deep margin. Microscopic examination showed a tumour composed of small uniformly sized blue neoplastic cells with round oval nuclei, scant cytoplasm, distinct nuclear membranes, finely dispersed nuclear chromatin, and inconspicuous nucleoli. Mitotic figures and individually necrotic cells were present.

The neoplastic cells showed positivity for cytokeratin 20 (CK20) in a perinuclear dot-like fashion, para keratin and synaptophysin. TTF-1 was negative. On the basis of immunohistochemical staining, the diagnosis of Merkel cell carcinoma was made. Lateral margins were clear, depth was clear with in 5 mm.

Laboratory work-up including complete blood count, renal, bone, hepatic and coagulation were all within normal limits. Computed tomography (CT) scan did not show any regional lymphadenopathy.

Radiation oncology was consulted given that the size and depth of the lesion. Radio-therapy was booked three weeks status post WLE.

Clinical features

The clinical presentation of MCC is relatively nonspecific. It typically presents as a painless, non-tender, firm, shiny violatious rapidly growing nodule, <2cm in diameter on sun exposed area. The surface of the nodule may be acneiform, telangiectatic or have an ulcer.[11]

The acronym AEIOU is helpful to recall the significant MCC clinical features: Asymptomatic, Expanding, Immunocompromised, Older than 50 years and UV exposed fair skin. The acronym is a sensitive screening tool with 89% of primary MCC patients having three or more of these findings.[12]

Although sun exposed areas are most frequently affected, all regions have been involved. At the time of presentation approximately 66% have only a cutaneous lesion (primary disease), 27% have regional LN metastasis and 7% have distant metastasis. Moreover of those MCC patients who present with visceral or LN metastasis 14% have an unknown primary tumour.[13]

Diagnosis

The low incidence of MCC coupled with its characteristic asymptomatic and painless early stages can pose significant challenges to making the diagnosis. Early diagnosis is imperative given the overall poor prognosis.

Regional LN involvement is frequently observed early on, often in absence of local invasion. Lymphadenopathy should be clinically, radiologically (usually CT) and cytologically (fine needle aspiration) assessed.

Definitive diagnosis requires tissue diagnosis usually after an incisional biopsy.

MCs cannot be identified by standard stains (e.g. hematoxylin-eosin) on light microscopy because of their similarity to other neuroendocrine cells. Therefore immunohistochemestry or electron microscopy analysis is required. Given that these cells synthesize and secrete numerous neuropeptides, identification of specific peptides (e.g. cytokeratin-20 and thyroid transcription factor-1) are required in MCC diagnosis.[1]

Three MCC histological subtypes have been described are: small cell, trabecular and intermediate (most common). These variants seem not to impact on prognosis.[14]

Staging

MCC follows the Halsteidian model of metastatic dissemination with a stepwise progression from local disease to regional LNs and hematological dissemination.[15]

Patients may be staged according to the American Joint Committee on cancer staging system or the 4 tier system staging system from Memorial Sloan-Kettering Cancer Center; see Table 1.[16]

Advanced imaging such as CT and MRI allows for more precise metastatic detection and may be helpful in localizing a MCC with unknown primary tumour.[17]

Treatment

MCC rarity makes large randomized clinical trials assessing various regimens of treatment almost impossible. Treatment is therefore somewhat pragmatic depending on the clinical stage and usually includes a combination of surgical excision and radiation, with chemotherapy added for metastatic disease.

The mainstay of treatment is excision either as wide local excision (WLE) or as MOHs chemosurgery.[18] Bichakjian and colleagues[19] recently reviewed the published literature on the surgical treatment of MCC and survival and concluded that the size of the tumor should determine the width of the excision margin with a margins of 1 cm are being recommended for tumors smaller than 2 cm, and margin of 2 cm being recommended for larger tumors, see Figure 1.

Algorithm for the management of Merkel cell carcinoma (± indicates with or without) from Bichakjian *et al.,* 2007.

To our knowledge no controlled trials have compared different excisional margins and MOHs. Despite the limited data, and their likely bias toward smaller lesions, local recurrence rates after MOHs surgery (4-8%) are comparable to those reported with WLE by several groups (4-14%).[20-22]

Prognosis and follow up

MCC generally has a poor prognosis with somewhat variable reported survival rates. MCC recurrence is commonly cited at 40%. It recurs locally in 25-30%, regionally in 52-59%, and distantly in 34-36%.[21,23,24] The mean time to relapse is eight months with 90%

Table 1: Four-Tier Staging System for Merkel Cell Carcinoma

Stage	Diagnosis	Localized Disease	Lymph node	Metastasis
I	Primary lesion <2 cm	Positive	Negative	Negative
II	Primary lesion >2 cm	Positive	Negative	Negative
III	Positive lymph node	Positive/negative	Positive/negative	Negative
IV	Distant metastasis	Positive/negative	Positive/negative	Positive

recurring within two years.[20,21,23] A single centre study put two-year mortality at 28% and the 10-year relative survival rate, based on tumor size of >2 and <2cm at about 60% and 40% respectively.[20] Remarkably, for a small tumor with a microscopically negative sentinel LNs, 5-year mortality is 21 percent.[19]

Histological staging of the lymph nodes is a significant predictor of the outcome. Additional factors such as primary tumor thickness, lymphocyte infiltration, histological growth pattern, lymphovascular invasion, size of the tumor nests in the lymph nodes, and extracapsular extension are under investigation in their relevance to the prognosis of this tumor.[19] National Comprehensive Cancer Network guidelines recommend follow-up visits every 1 to 3 months during the first year, every 3 to 6 months during the second year, and every 6 to 12 months thereafter.[25]

Discussion

MCC is found mostly on skin-damaged and sun-exposed including the face, head, and neck (55%), the extremities (40%) and truncal

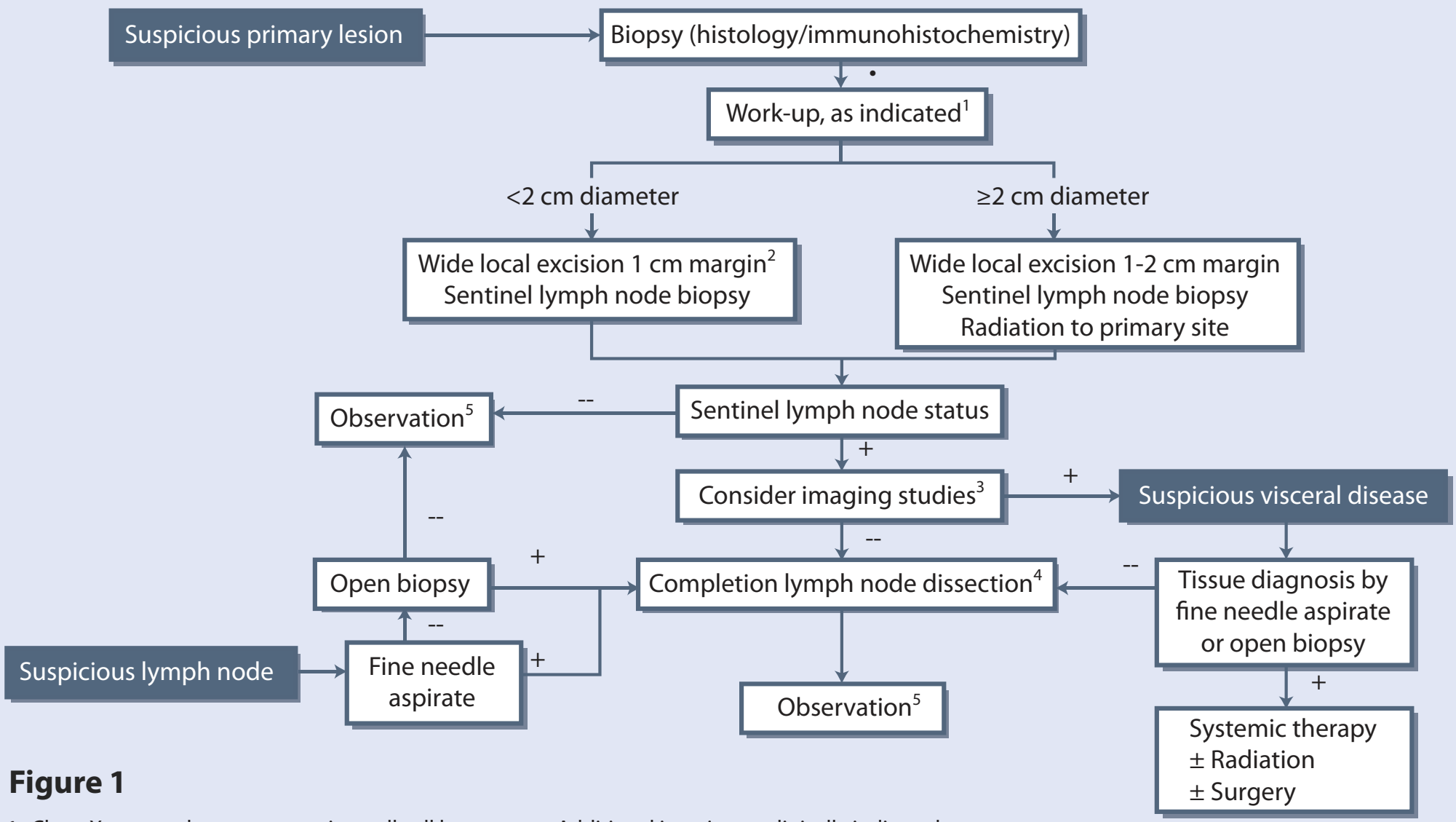


Figure 1

1. Chest X-ray to rule out metastatic small cell lung cancer. Additional imaging as clinically indicated.
2. Adjuvant radiation to primary site if negative surgical margins cannot be obtained. Margins may be modified in certain anatomic locations.
3. Computed tomography chest, abdomen, pelvis: magnetic resonance imaging brain: consider positron emission tomography.
4. Consider radiation as primary therapy if not a surgical candidate or if minute tumor burden in sentinel lymph node. Consider radiation following completion lymph node dissection if extracapular nodal extension present.
5. History and physical exam every 2-6 months for 2 years, every 6-12 months thereafter. Additional imaging as clinically indicated.

SUMMARY OF KEY POINTS

Asymptomatic rapidly growing violatious nodule on sun exposed are in caucasion males over 60 years think Merkel cell carcinoma.

Merkel cell carcinoma is chemosensitive immediate referral to plastic surgery must be considered.

Identification is key to survival; the only independent prognostic indicator known is disease stage at presentation.

structures (5%) with occurrence on non-sun exposed sites being extremely uncommon.[26]

MCC has a propensity for local recurrence, regional lymph node (LN) and distal metastasis, particularly to the lung, liver, brain, bone and skin. It predominantly affects elderly Caucasians with a mortality rate of 33%.[12]

IHC with or without EM is required to diagnose MCC. To date, the only factor significantly associated with overall survival is the stage of disease at presentation.[16] This makes early diagnosis and treatment imperative.

There are no standard treatment protocols for MCC. Treatment regimens found in the literature are based on the extent of disease local, regional or distant. Surgery and Radiotherapy play a fundamental role in the management of local disease. Recurrence rates are comparable between WLE and MOHs. Adjuvant RT is shown to improve survival in tumors of all sizes with greatest impact on survival where tumours were > 2 cm[1] A meta-analysis found an improvement regional recurrence rates when resection of regional LN basin complimented with radiotherapy.[19] However there is little data supporting the use of adjuvant RT to the surgical bed in the treatment of primary MCC.

MCC is a relatively chemosensitive tumor with initial overall

CLINICAL PEARLS

MCC thought of as a local disease. However its is a systemic disease. Systemic therapy is often required.

Prior radiation therapy is not a known MCC risk factor

response rates of approximately 60-70%. There is no standard therapeutic regimen for metastatic disease. Despite this distant disease is poorly controlled.[19] This in turn results in controversy regarding overall disease management.

MCC IS A RELATIVELY CHEMOSENSITIVE TUMOUR WITH INITIAL OVERALL RESPONSE RATES OF APPROXIMATELY 60–70%.

In summary, the MC is a fascinating cell about which much is still being learned. They give rise to Merkel cell carcinoma which is a very aggressive tumour with a poor prognosis. Early treatment is of the utmost importance to improve survival rates.

The authors have no competing interests to declare.

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