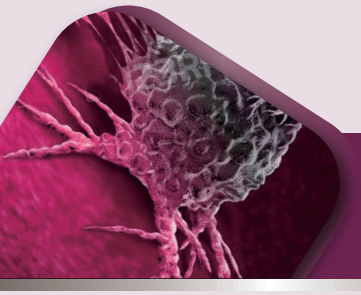
默克細胞癌

MERKEL CELL CARCINOMA

— Overview, Specialists' Perspectives and Case Reports

〖中英對照〗



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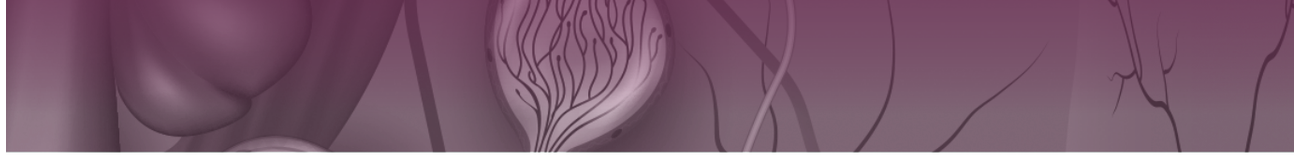

1 Introduction

Dr. John Wen-Cheng Chang/
President of Taiwan Society for Immunotherapy of Cancer

In 1972, Cyril Toker first described a trabecular carcinoma of the skin[1]. Six years later, the expression of phenotype identified by Tang and Toker led to a hypothesis that the skin trabecular carcinoma originates from Merkel cells[2]. Finally, immunohistochemical analysis supports this hypothesis[3]. The name, Merkel cell carcinoma (MCC), was formally proposed by De Wolff-Peeters in 1980 and remained the most commonly used and accepted term[4].

The incidence rate of MCC has increased over the past two decades. The number of MCC cases reported annually in the United States increased by 95% from 2000 to 2013, and the incidence rate came to 0.7 cases/100,000 person-years in 2013[5]. However, there were few publications of MCC in non-Caucasian populations, and the incidence rate of MCC in Asian countries is yet to be determined. MCC is an aggressive neuroendocrine tumor and has poor survival rates. Of MCC patients, 25-50% might develop recurrence, and 5-year relative or MCC-specific survival rates range from 41% to 77%[6].

Several treatments are used for MCC, including surgery, chemotherapy, radiotherapy and immunotherapy. Approved these years, immunotherapeutic agents are new treatments that have made a big difference to MCC treatment and improved treatment outcomes, as discussed in the following chapters. MCC needs to be diagnosed correctly and treated efficiently because it is rare and prone to be ignored. Besides, relevant reports are limited in Asian countries. This book presents studies and cases in attempt to bring health care providers more information about MCC from specialists' perspectives, so as to improve MCC patients' survival and even quality of life.

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Expert's Opinion

Article citations: 2019 TSITC Skin Cancer Forum Keynote Speech

Insights and Advances in the Treatment of Merkel Cell Carcinoma

Speaker : A/Prof. Shahneen Sandhu/
Peter MacCallum Cancer Centre, Melbourne

Merkel cell carcinoma (MCC) is a rare, aggressive neuroendocrine skin cancer[1]. At the time of presentation, the vast majority of MCC patients present in local rather than regional or metastatic disease. MCC is associated with poor survival outcomes[2].

MCC may associate with Merkel cell polyomavirus (MCPyV) infection[3]. MCPyV infection may cause genetic mutation of RB domain, which may result in RB disfunction and MCC tumorgenesis[4]. For viral-negative tumor, a high frequency of mutations in RB1, TP53, NOTCH1, and FAT1 is observed. Recent study also shows that viral-negative tumors manifest a high tumor mutational burden related to UV-induced DNA damage signature. In contrast, viral-positive tumors may express low mutation rates[5].

Sentinel node biopsy (SLNB) is recommended for all MCC patients without regional lymph node disease or distant metastasis due to aggressive disease characteristics. Even for patients with a tumor size <1 cm, the positive sentinel node status (PSLN) rate reaches 23.8%. For tumor size of 1-2 cm and >2 cm, PSLN rate are 58.6% and 68.2%, respectively[6]. SLNB should be used as an evaluation for treatment and surveillance plan. For patients with a negative SLNB, de-escalation of treatment may be considered.

Chemotherapy was the mainstay of treatment for unresectable and/or metastatic MCC (mMCC). mMCC is chemosensitive, however, responses are seldom durable and overall prognosis was poor[7-8]. Until recently, studies indicate that mMCC is an immunogenic tumor with high incidence of tumor infiltrating lymphocytes (TILs), which provides a rationale for using immune-checkpoint inhibitors (ICI) in MCC treatment[9]. Several clinical trials, including JAVELIN Merkel 200, KEYNOTE-017, and CheckMate 358, investigate the efficacy of ICI in mMCC treatment[10-13]. From these studies, ICIs show promising efficacy in mMCC with early and durable responses as well as limited toxicity. Biomarkers and clinical predictors of ICI responder are being explored, and novel combinations with other treatment modalities, such as RT, are under active investigation.

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2 *From Specialist's Perspective*

2-1 Dermatologist's Perspective

Dr. Yao-Yu Chang/Linkou Chang Gung Memorial Hospital

Introduction

Merkel cell carcinoma (MCC) is a rare cutaneous malignancy, and most commonly appears in elderly people with light skin types. It is highly aggressive, and with tendencies of recurring after excision and metastasis to regional lymph nodes.

Risk factors

MCC predominantly affects people with light skin. Approximately 95 percent of cases arise in the white population[1]. It is exceedingly rare in east Asian population. Between 1970 and 2009, only 22 cases were identified out of 3,100,000 pathology database and medical records from 18 cancer or dermatology hospitals in China[2].

It is typically seen in elderly people with the mean age of 74 years for men and 76 years for women at diagnosis[1]. Immunosuppressed subjects, including organ transplant recipients, HIV-positive individuals, and those with B cell malignancies also have higher incidence, and tend to be diagnosed at a younger age[3-5].

Clinical features

The tumor favors sun-exposed area such as head and neck, followed by the extremities and buttocks. It usually presents as a pink-red to violaceous, dome-shaped, firm, solitary nodule, and grows rapidly (Figure 1). Ulceration is not uncommon (Figure 2). Overall, the behavior of MCC is very aggressive, with significant risk of local recurrence after excision.

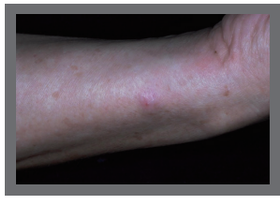

Figure 1. A skin-colored to pink papule on the dorsal forearm. It is likely to be misdiagnosed as a benign skin growth.

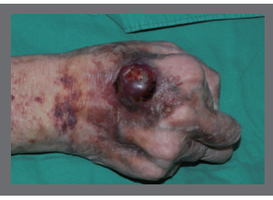

Figure 2. An ulcerated, red to violaceous rapidly growing tumor on the right dorsum of the hand.

In an analysis of 9,387 MCC cases from the National Cancer Database in the US between 1998 and 2012, median age of diagnosis was 76 years, with 88% aged more than 60 years and 70% aged more than 70 years. The most frequent anatomic locations for the primary tumor were the following[6]:

- Head and neck: 43%
- Upper limbs and shoulder: 24%
- Lower limbs and hip: 15%
- Trunk: 11%
- Other areas: 7%

Diagnosis

Merkel cell carcinoma is often misdiagnosed as a benign cyst, lipoma or pyogenic granuloma. A high index of suspicion is required when dealing with patient with the following features, identified by analysis of a series of 195 cases diagnosed in a period of 27 years[7]:

- **A**symptomatic or lack of tenderness
- **E**xpanding rapidly
- **I**mmune suppression
- **O**lder than 50 years old
- **U**ltraviolet-exposed area on a person with fair-skin

These features can be easily memorized by the acronym AEIOU. The presence of 3 or more of these features indicates the higher possibility of MCC. Biopsy and histologic examination are necessary to establish the diagnosis.

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2-2 Pathologist's Perspective

Dr. Yen-Lin Huang/Linkou Chang Gung Memorial Hospital

Merkel cell carcinoma (MCC) is a rare but highly aggressive skin cancer with neuroendocrine features; it is most prevalent in Caucasian men in their seventies, typically affecting chronically sun-damaged areas, such as the head/neck and exposed limbs.

Besides chronic exposure to ultraviolet irradiation, the pathogenesis of MCC is also associated with Merkel cell polyomavirus (MCPyV) infection. MCPyV-positive patients account for approximately 80% of MCC cases, are usually younger than average and are equally likely to have MCC affecting the head/neck or extremities, although non-sun-exposed sites are sometimes involved. MCPyV-negative MCC is more common in sun-damaged skin of the head/neck comorbid with other non-melanoma skin cancers, for example, basal cell carcinoma or squamous cell carcinoma. A few patients present with metastatic MCC from a primary lesion that may be unknown or have regressed.

Histologically, MCC is predominantly dermal but infiltrates subcutaneous tissues, with a discernable border. MCC cells form solid sheets or, less commonly, show a trabecular or organoid growth pattern. Although the overlying epidermis is spared by a grenz zone, up to 10% of cases have intra-epidermal spread that makes it difficult to distinguish MCC from Paget's disease, Bowen's disease, or malignant melanoma.

MCC cells are monomorphic small-to-medium-sized and atypical, with scant and round-to-oval nuclei, an abnormally high nuclear-to-cytoplasmic ratio and nuclear molding. Their nuclei have a finely granular 'salt-and-pepper' chromatin pattern, with multiple small nucleoli. Unusual cytological appearances include cells that are more discohesive, plasmacytoid with abundant cytoplasm, clear, or have spindled, or anaplastic features.

Immunohistochemically, MCC cells express neuroendocrine markers chromogranin A, synaptophysin, CD56 and neural markers such as neurofilament protein. They may also be positive for B cell lymphoma-2 (BCL-2), CD99, CD117, CD57, p63 (rarely), and terminal deoxynucleotidyl transferase (TdT), glypican-3, as well as epithelial markers, most commonly low molecular weight keratin (CAM5.2), epithelial membrane antigen (EMA), pan-cytokeratin antibody (AE1/AE3), and cytokeratins 7 (CK7) and 20 (CK20). Although CK20 expression is variable, most MCC cases are at least focally positive for CK20, typically with a paranuclear 'dot-like' or punctate pattern. However, other staining patterns, for example, membranous or cytoplasmic, may also be observed. MCC cells are usually negative for vimentin, S-100 protein and thyroid transcription factor-1 (TTF-1). The monoclonal antibody CM2B4 can be used to detect MCPyV.

The first question in differential diagnosis of MCC is whether it is primary or metastatic, such as small-cell neuroendocrine carcinoma of the lung (SCLC) that has metastasized to the skin. Helpful tools include clinical history, histology, and immunohistochemistry, primarily TTF-1, CK7, and CK20. Lack of diffuse immunoreactivity for TTF-1 and CK7 helps to differentiate MCC from primary SCLC. Besides SCLC, neuroendocrine carcinomas from other sites may also metastasize to the skin, and may also be immunonegative to TTF-1. Other site-specific markers and, most importantly, clinical history are fundamental to distinguishing metastatic neuroendocrine carcinomas from MCC.

The main features distinguishing MCC from melanoma or non-melanoma skin cancers include:

1. **Basal cell carcinoma (BCC)**: MCC lacks palisaded peripheral cells and displays characteristic neuroendocrine cytology. In addition, 'dot-like' CK20 staining strongly favors MCC, and MCPyV is negative in BCC.

2. **Melanoma**: small-cell variant occasionally enters the differential diagnosis of MCC. Large irregular nuclei with prominent nucleoli are unusual in MCC and melanin pigments favor melanoma, although melanophages may sometimes be seen in MCC. Immunohistochemistry can resolve the diagnoses in most cases of MCCs that are HMB-45 or other melanocytic markers negative and where melanoma is MCPyV negative.

3. **Ewing sarcoma (EWS)**: EWS is a small, round, blue cell tumor that may show strong membranous staining for CD99 and nuclear labeling for Friend leukaemia integration-1 (FLI-1). Most cutaneous EWSs show t (11; 22) by fluorescence *in situ* hybridization or reverse transcription polymerase chain reaction. All EWSs are immunohistochemically negative for MCPyV.

4. **Lymphoma** may mimic small-cell MCC morphologically and immuno-histochemically. PAX-5, TdT, CD56, and CD99 may be positive in both malignancies. Additional immunostaining, including CK20

and MCPyV, is needed to make a correct diagnosis.

5. **Sebaceous carcinoma**: periadnexal involvement and pagetoid intraepidermal spread can involve sebaceous carcinoma in the differential diagnosis of superficial MCC. Sebaceous carcinoma is usually adipophyilin-positive and negative for CK20 and MCPyV.

6. **Squamous cell carcinoma (SCC)**:SCC with neuroendocrine differentiation may be impossible to distinguish from MCC. If CK20 and two or more neuroendocrine markers are positive, these tumors are conventionally considered to be MCC.

As many as half of MCCs are unsuspected at the time of biopsy; the most important aspects of diagnosis are open-minded recognition that MCC is a possibility, and attention to the clinical description of a nodular lesion in the context of superficial biopsies. If the histopathologic findings don't match the clinical suspicion, more comprehensive investigations and asking the clinician to perform a deeper or excisional biopsy are strongly advised. Cytological neuroendocrine features apparent in a skin tumor require evaluation by CK20, as well as other markers of extracutaneous neuroendocrine carcinomas, including TTF-1. Immunohistochemistry for MCPyV is specific but not sensitive, and is not universally available.

Pathology reporting should include, but not be limited to, tumor size, peripheral and deep margin status, lymphovascular invasion, and the presence or absence of adjacent organ or tissue involvement. A second tumor, SCC or BCC should also be reported, if encountered.

Sentinel lymph node biopsy is often requested. For tumors that are not obvious at the morphological level, immunohistochemistry such as CK20 and/or CAM5.2 may be needed to identify scattered tumor cells. The American Joint Committee on Cancer recommendation for lymph node reporting includes the tumor burden, size, and the presence or absence of extranodal invasion.

NOTE

2-3 Oncologist's Perspective

Dr. Chiao-En Wu/Linkou Chang Gung Memorial Hospital

Merkel cell carcinoma staging

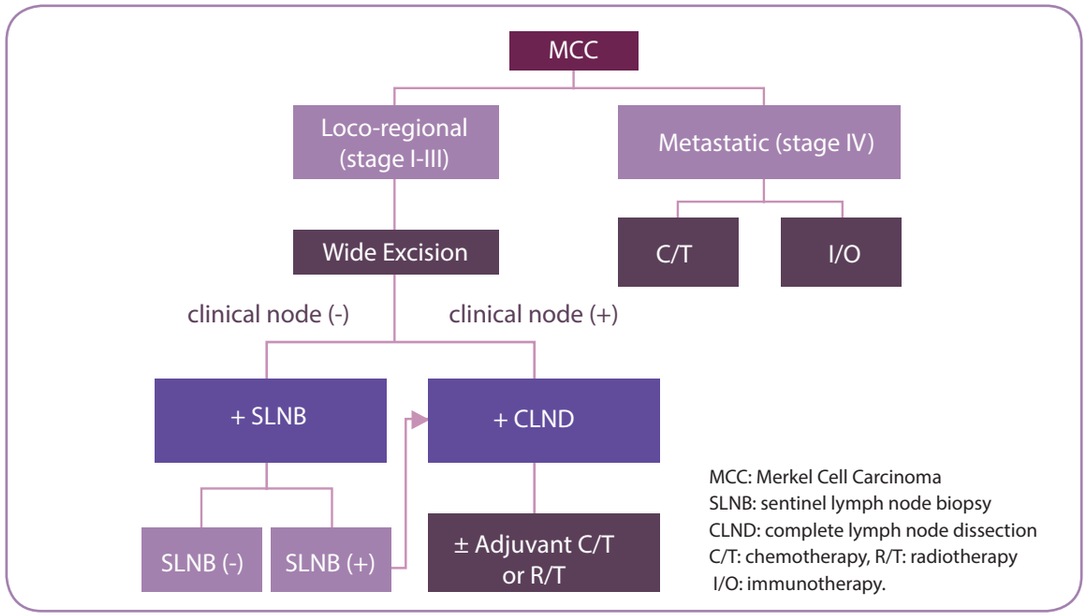
The American Joint Committee on Cancer TNM staging system, stages Merkel cell carcinoma (MCC) according to tumor size, regional lymph node involvement, and distant metastases (Table 1).

Table 1. Simplified staging of MCC

Stage	T (Primary tumor)	N (Regional lymph node)	M (Distant metastasis)
I	≤2 cm	No	No
II	>2 cm	No	No
III	Any	Yes	No
IV	Any	Any	Yes

Treatment intervention

Figure 1. MCC treatment is stage dependent



Loco-regional MCC

Aggressive surgical intervention, such as wide excision and lymph node management (sentinel lymph node biopsy for node-negative MCC or complete lymph node biopsy for node-positive MCC), is critical to achieving better survival rates in patients with loco-regional MCC (stage I-III)[1]. Moreover, salvage surgery for loco-regional recurrence is effective. Patients at high risk of recurrence might be given adjuvant radiotherapy or chemotherapy despite remaining uncertainty about the role of adjuvant treatment.

Metastatic MCC

Before the advent of immunotherapy, the initial treatment of metastatic MCC generally involved palliative chemotherapy with cisplatin and etoposide; although the cyclophosphamide, doxorubicin, and vincristine regimen were an alternative, chemotherapy had limited benefit in this setting.

Since then immune checkpoint inhibitors – avelumab, pembrolizumab, and nivolumab – have been shown to produce durable response in patients with metastatic MCC. The U.S. Food and Drug Administration (FDA) has approved all three; however, avelumab was the only checkpoint inhibitor the Taiwan FDA had approved for metastatic MCC by May 2019.

Efficacy and safety of checkpoint inhibitors vs chemotherapy (historic data)

Avelumab had favorable efficacy and safety in MCC patients with durable response, including 88 chemotherapy-refractory patients (response rate: 34%)[2,3] and 39 chemotherapy-naïve patients (response rate: 62.1%)[4]. Compared with conventional chemotherapy, avelumab had higher response rates and more durable antitumor activity. Avelumab is therefore considered standard of care for metastatic MCC in Taiwan.

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3 *Case Report*

3-1 Case Report 1: 82-year-old man with a thigh tumor and inguinal lymphadenopathies

Dr. Yao-Yu Hsieh/Taipei Medical University-Shuang Ho Hospital

Background

An 82-year-old man with a history of thymoma was treated with Mestinon® (pyridostigmine) supplement after a thymectomy 25 years ago. He presented to the dermatology outpatient clinic with symptoms of a right thigh tumor, which had begun 3 years earlier; his tumor had grown, especially over the past 6 months. The patient denied other associated symptoms or signs, such as diaphoresis, poor appetite, night fever, or weight loss.

Diagnosis and procedure

Physical examination discovered a freely movable, bluish, indurated mass, about 2 cm wide; there was no local tenderness or heat and he therefore had an en bloc resection.

The pathologist reported primary neuroendocrine carcinoma of the skin, pT1NxMx, stage I with margin involvement. Detailed investigations revealed high mitotic activity (>30/10 high-power field), lymphovascular invasion, cytokeratin 20 and synaptophysin positivity, but negative results for CD45, vimentin, S100, paired box gene 8, thyroid transcription factor 1, and cytokeratin 7. He refused another surgery.

Two months post-surgery, an inguinal mass appeared. Pelvic computed tomography (CT) at the general surgery outpatient clinic, detected right inguinal lymphadenopathies (Figure 1). Following right inguinal lymph node dissection, he was referred for radiotherapy, during which right inguinal swelling and leg edema were noted. CT images showed recurrence of lymphadenopathies and para-aortic lymphadenopathies with inferior vena cava compression (Figure 2a & 2b). He was referred for palliative cancer treatment.

Palliative treatment

Given the patient's age, we recommended avelumab after consulting himself and his family; however, treatment was not commenced immediately. Due to worsening leg swelling, he was given dose-adjusted cisplatin and etoposide; the swelling diminished after the first chemotherapy cycle, but he relapsed soon after the second cycle. Consequently, he had to walk with a crutch and had Eastern Cooperative Oncology Group performance status of 2. We added avelumab to his third course of chemotherapy, but he developed neutropenic fever with sepsis (*Escherichia coli)* after then and we administered only avelumab from the fourth treatment course.

After three courses of avelumab, CT re-staging indicated a partial response, and he could walk without a crutch (Figure 3a & 3b). Re-staging after six treatment cycles showed liver metastases. After discussion with our patient and his family, we suggested hospice care. He died 2 months after the last avelumab dose. There was no immune-related adverse event during the six courses of avelumab.

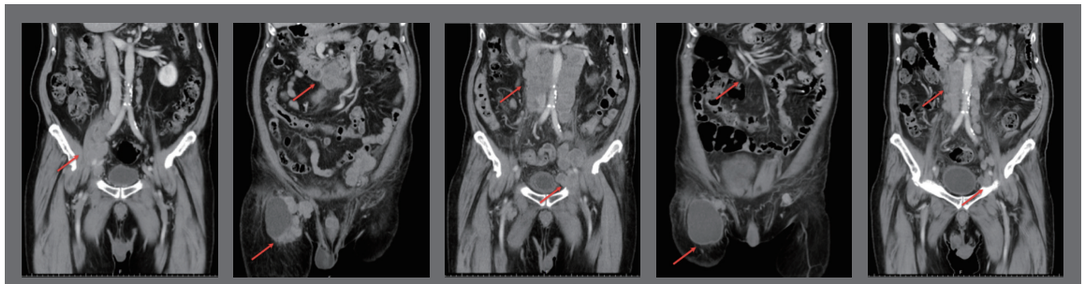


Figure 1 | Figure 2a | Figure 2b | Figure 3a | Figure 3b

3-2 Case Report 2 : 75-year-old man with recurrent Merkel cell carcinoma on the back

Dr. Chang-Hsien Lu/Chiayi Chang Gung Memorial Hospital

Presentation, diagnosis and treatment

A 75-year-old man who had undergone laser prostatectomy for benign prostate hyperplasia, and had chronic renal insufficiency, was admitted to the plastic surgery ward with a 3.5 by 3 cm red, indurated progressive mass with keratotic changes over his right upper back. Biopsy pathology diagnosed invasive carcinoma with neuroendocrine characteristics. Abdominal computed tomography (CT) and chest X-rays showed no evident lesions. Wide excision of the back tumor, with free margin, was done in May 2014. Detailed pathology reported Merkel cell carcinoma, pT2, with focal epidermal squamous cell carcinoma *in situ* and positive immunohistochemistry (IHC) for chromogranin, synaptophysin, CK20, epithelial membrane antigen and CD117.

This patient was subsequently lost to follow-up until February 2017, when he visited the Emergency Department with a progressive mass over right axillary area, which had begun more than 1 year previously, accompanied with marked right arm lymphedema and numbness. Biopsy pathology showed metastatic Merkel cell carcinoma with paranuclear dot-like pattern of CK20 IHC positivity. CT showed an unresectable mass over the right axillae, with chest wall invasion and vessel encasement but no distant metastases (Figure 1).

Because of his frail and elderly condition, chemoradiotherapy with weekly platinum and radiotherapy (5,500 cGy in 20 fractions) was used for local disease control, which only achieved minor tumor regression. Further chemotherapy with concurrent platinum and etoposide was used for 6 cycles between May and September 2017. Despite marked tumor regression, his right arm lymphedema and numbness persisted (Figure 2). Oral etoposide was prescribed for 1 week as maintenance therapy, but he had intolerance, with generalized skin itchy.

This patient enrolled in the global avelumab early access program in 2018. Biweekly avelumab began on 8 May 2018 and he tolerated this treatment well; his right arm lymphedema resolved after 2 cycles. No immunotherapy-related adverse event or obvious side effects except mild leukocytosis developed. The serial follow-up image studies showed stable disease (Figure 3). He remains on avelumab treatment.

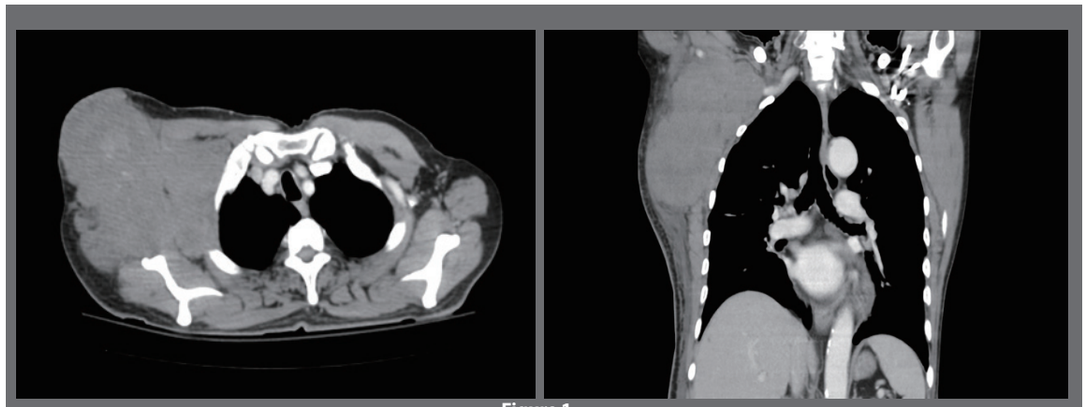


Figure 1

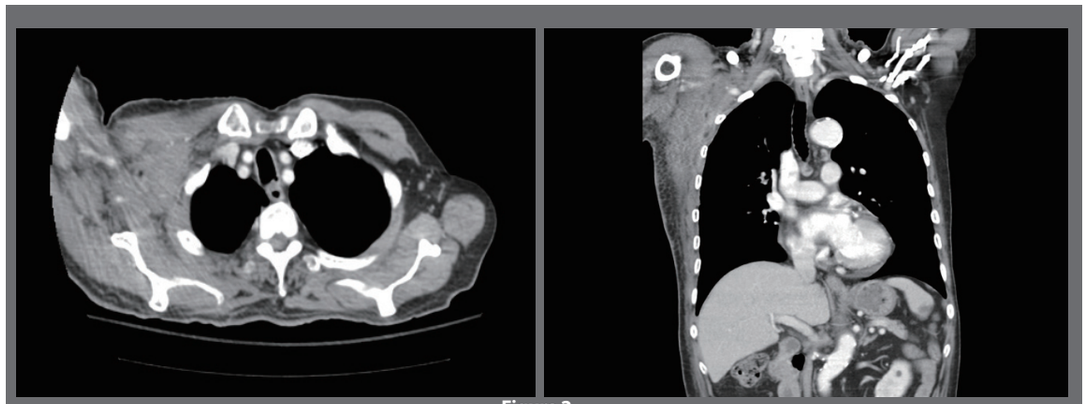


Figure 2

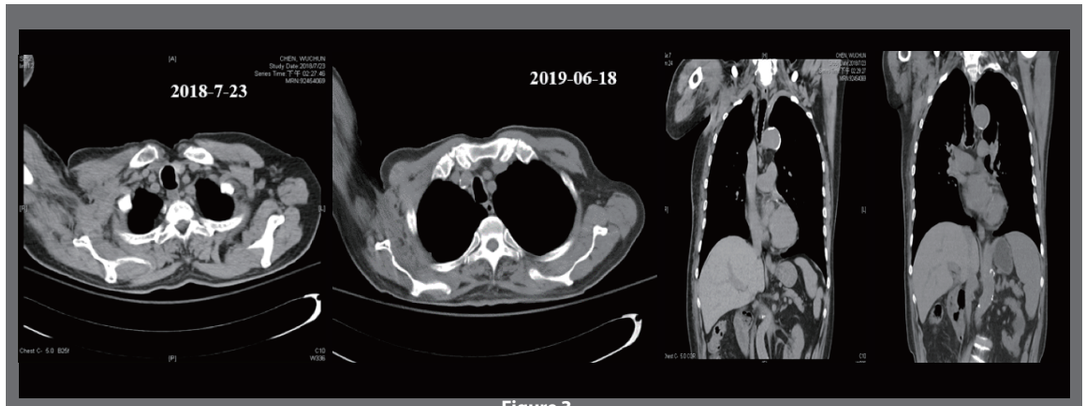


Figure 3

3-3 Case Report 3 : 75-year-old man with right lower leg swelling

Dr. Jui-Hung Tsai/National Cheng Kung University Hospital

Background

A 75-year-old man with coronary artery disease had coronary artery bypass surgery and a pacemaker implanted. He had a history of type 2 diabetes mellitus, hypertension, and stage 3 chronic kidney disease (serum creatinine 1.6 mg/dL). His initial presentation was right lower leg swelling for 2 weeks and a right inguinal mass noted on admission. We initially treated this as cellulitis but as there was no improvement, and then did a more detailed examination.

Diagnostic workflow

Lower extremity color duplex ultrasound showed an inguinal mass about 10 by 7 cm, which was biopsied and shown to be a small-cell carcinoma (strongly positive for chromogranin and synaptophysin, positive for cytokeratin by dot-like staining, and negative for leukocyte common antigen and thyroid transcription factor 1). We did a whole body computed tomography scan, panendoscopy and colonoscopy to rule out small-cell carcinoma of lung or gastrointestinal origin; no other suspected lesion was found. Consultation with the pathologist confirmed the diagnosis of Merkel cell carcinoma (MCC).

Treatment

At diagnosis in March 2017, we performed local radiotherapy with 6,900 cGy/30 fractions together with systemic chemotherapy with etoposide/carboplatin (1 cycle during radiotherapy and another 3 cycles afterwards). The tumor showed a partial response to four cycles of chemotherapy. Because of cytopenia and intolerable adverse effects, we withheld chemotherapy. MCC remained stable for 1 year, but then progressed; etoposide/carboplatin re-challenge only had a limited effect. From October 2018, we applied for avelumab on a compassionate use basis. The initial response to avelumab monotherapy was stable disease after 6 cycles. The leg swelling progressed again, so we added oral topotecan from December 2018, after which grade 3 anemia and neutropenia were noted. Gradually diminished tumor size and leg edema were noted thereafter.

Current condition

This patient continues to receive avelumab 10 mg/kg every 2 weeks and oral topotecan 1 mg daily for 4 days each cycle (up to 18 cycles through June 2019 and ongoing). Adverse events include grade 3 anemia requiring monthly transfusion, grade 2 neutropenia that does not require G-CSF use, grade 1 thrombocytopenia, and grade 1 nausea. Immune-related adverse events include grade 2 skin rash requiring systemic antihistamine and topical steroid.

3-4 Case Report 4 : 78-year-old-man with Merkel cell carcinoma recurrence at the left thigh

Dr. Yu-Li Su/Kaohsiung Chang Gung Memorial Hospital

Background

In 2015, a 78-year-old man visited the plastic surgery clinic due to an obvious and growing mass on the left heel that had first appeared several months earlier; he was in a good physical condition with no other appreciable disease. The protuberant and indurated, mass was 5-6 cm wide (Figure 1) and skin biopsy confirmed the diagnosis of Merkel cell carcinoma (MCC). Computed tomography (CT) imaging discovered obvious left inguinal and pelvic cavity lymphadenopathies (Figure 2).

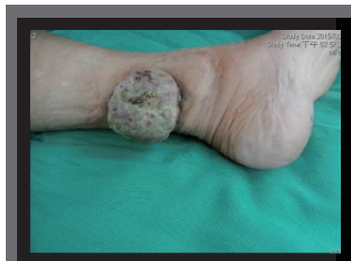


Figure 1

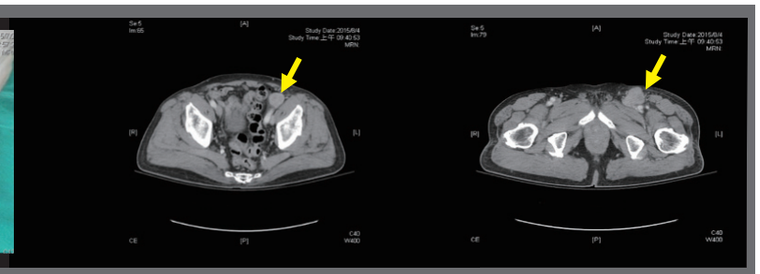


Figure 2a

Figure 2b

In August 2015, the patient underwent wide resection of the left heel tumor, inguinal and pelvic cavity lymph node dissection, and free posteromedial thigh flaps transplantation. Post-surgery pathology reports affirmed that the primary MCC tumor was more than 5 cm across (T3) and had spread to pelvic cavity lymph nodes; it was accordingly categorized as pT3N1M1, Stage IV. The surgical wound healed well and radiotherapy (4,000 cGy in twenty fractions) was then performed on the primary tumor and metastatic lymph node regions.

Clinical features and diagnostic workflow

After radiotherapy, the patient remained disease-free until August 2018, when he returned with several differently sized red masses on the left thigh (Figure 3). Dermatological biopsy confirmed recurrence of MCC. Microscopy revealed small, round neoplastic cells, and immunohistochemistry was positive for CK20, CD56, synaptophysin and chromogranin A. CT of the pelvis ruled out metastasis to other organs.

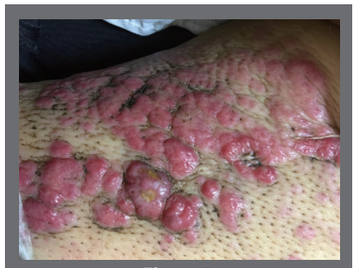


Figure 3

Treatment

The man was treated with oral etoposide 100 mg/day for 3 days and intravenous cisplatin at 50 mg/m^2 every 3 weeks. Meanwhile, an application to use avelumab was submitted. The skin tumor started to regress after two chemotherapy cycles (Figure 4b) and after two more cycles, the treatment was changed to avelumab. The patient responded well to avelumab and the tumor continued to regress during three cycles of avelumab. The last time he visited the clinic, the patient showed a complete clinical response with no obvious skin lesion (Figure 4c).

Besides anemia, there were no other adverse hematological events during chemotherapy. The patient complained about fatigue and loss of appetite, but had good tolerance to avelumab, with no treatment-related adverse events.

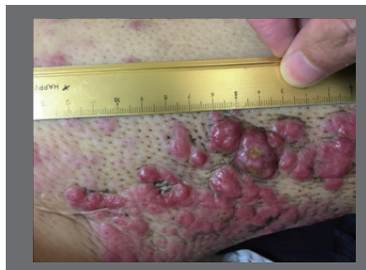


Figure 4a. Before treatment

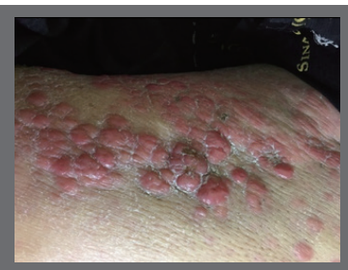


Figure 4b. After chemotherapy

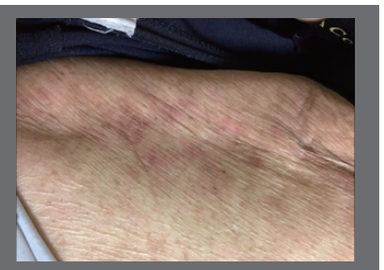


Figure 4c. After avelumab treatment

Follow-up status

The man's family could not afford ongoing hospital care and decided to transfer him to a nursing home and to discontinue avelumab. During his stay at the nursing home, choking caused aspiration pneumonia. He was brought to the emergency department with dyspnea but based on his do-not-resuscitate agreement, no further treatment was given. He died two days later.

4 Novel MCC Therapy with Avelumab

Dr. Chiao-En Wu/Linkou Chang Gung Memorial Hospital

What is avelumab?

Avelumab is an immune checkpoint inhibitor; this fully human monoclonal antibody inhibits the interaction between PD-L1, the immunomodulatory cell-surface programmed death-ligand 1, and its receptor (PD-1), but does not block the PD-L2/PD-1 pathway[1,2]. PD-L1 expression has been observed in Merkel cell carcinoma (MCC) cells, as well as nearby infiltrating immune cells.[1,2] Avelumab has been approved in Taiwan since 2018, and is indicated as monotherapy to treat metastatic MCC in adults.[2,3] The recommended regimen is 10 mg/kg body weight avelumab administered intravenously over 60 minutes every 2 weeks.[2]

JAVELIN Merkel 200 trial: parts A & B

JAVELIN Merkel 200 is a multicenter, single-arm, open-label, phase 2 clinical trial. Patients aged ≥18 with stage IV histologically confirmed MCC were enrolled, irrespective of PD-L1 expression or Merkel cell polyomavirus status. Participants received 10 mg/kg avelumab by intravenous infusion over 1 hour every 2 weeks until they either withdrew or developed intolerable adverse effects or disease progression. Separate parts of the clinical trial analyzed patients in two subgroups, 88 who had already received chemotherapy for metastatic disease (Part A), and 39 who had not (Part B).

Part A: previously treated patients [2]

In Part A, the primary endpoint was confirmed best overall response, defined as complete response, partial response, stable disease, or progressive disease. The median age of 88 patients was 72.5 years; all had received at least one previous line of treatment for distant metastases. Twenty-eight (31.8%) achieved an objective response, including eight complete and 20 partial responses, and another nine achieved stable disease. Sixty-two (70%) developed treatment-related adverse events, predominantly grade 1–2. Four patients had five grade 3 events, but none had treatment-related grade 4 or worse events. These results suggested that avelumab is efficacious and well-tolerated in patients with chemotherapy refractory metastatic MCC, even elderly ones.

Part A: long-term follow-up

In another analysis, after a median follow-up of 16.4 months[4], the objective response rate was 33.0%, with 10 complete and 19 partial responses. The median progression-free survival (PFS) and overall survival (OS) were 2.7 months and 12.9 months respectively, and the 1-year PFS and OS rates were 30% and 52%. These encouraging findings indicate that avelumab might offer potential long-term benefit for patients with metastatic MCC progression after chemotherapy.

New efficacy data on patients with ≥2 years of follow-up[5], showed that the PFS rate kept stable–29% at 1 year, 29% at 18 months, and 26% at 2 years (Figure 1); median OS was 12.6 months and the 2-year OS rate was 36% (Figure 2). These results provide evidence of avelumab's continued durable responses and meaningful survival outcomes in patients with metastatic MCC.

Figure 1. Progression-free survival with avelumab in metastatic Merkel cell carcinoma

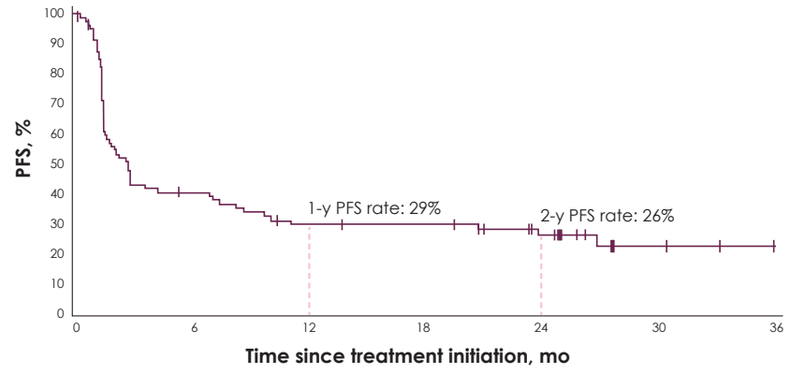
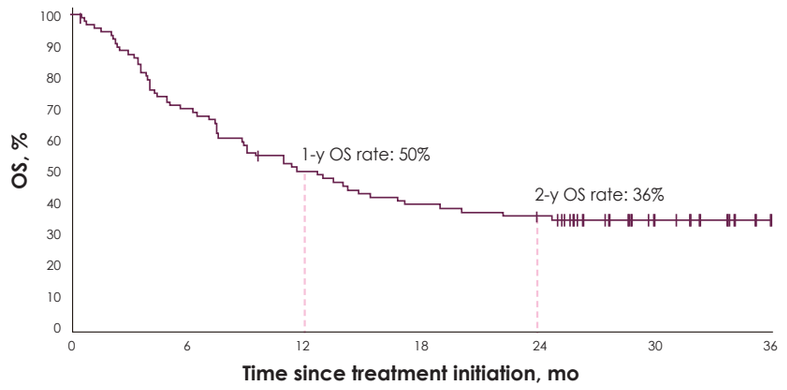


Figure 2. Overall survival with avelumab in metastatic Merkel cell carcinoma



Part B: treatment-naïve patients[6]

JAVELIN Merkel 200 enrolled 39 patients naïve to treatment for metastatic disease to assess the efficacy and safety of avelumab in the first-line setting. The primary endpoint was durable response, defined as an objective response with a duration of at least 6 months. These patients' average age was 75 years; 29 were followed up for at least 3 months, and 14 for at least 6 months. Eighteen (62.1%) achieved an objective response (four complete and 14 partial responses) and 24 (83%) showed durable responses. Among the 14 patients with a 6-month or longer follow-up, an objective response rate of 71.4% (four complete and six partial responses) and a durable response rate of 89% were reported. Twenty-eight (71.8%) of the 39 patients developed treatment-related adverse events: eight had grade 3 events, but none had grade 4 or worse events. First-line avelumab treatment produced high response rates with satisfactory tolerance in patients with metastatic MCC.

Table. Summary of first-line and second-line treatment efficacy

	First-line treatment[6]		Second-line treatment[4,5]	
Medium duration of follow-up	≥3 mo (N=29)	≥6 mo (N=14)	≥1 year (N=88)	≥2 year (N=88)
ORR, %	62.1	71.4	33.0	33.0
CR	13.8	28.6	11.4	11.4
PR	48.3	42.9	21.6	21.6
SD	10.3	7.1	10.2	10.2
PD	24.1	14.3	36.4	36.4
Not evaluable	3.4	7.1	20.5	20.5
mDOR (95% CI) Range, mo	NE (4.0-NE)	NE (4.0-NE)	NE (18.0-NE), 2.8-23.3+	NR (18.0-NE), 2.8-31.8+
Proportion of response with duration ≥6 mo (95% CI), %	83 (46-96)	89 (43-98)	93 (74-98)	—
mPFS (95% CI), mo	9.1 (1.9-NE)	—	2.7 (1.4-6.9)	—
mOS (95% CI), mo	NE	—	12.9 (7.5-NE)	12.6 (7.5-17.1)

CR, complete response; DOR, duration of response; NE, not estimable; NR, not yet reached; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; SD, stable disease.

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5 Conclusion

Dr. Chia-Yu Chu/National Taiwan University Hospital

Merkel cell carcinoma (MCC) is a rare but highly aggressive skin cancer that carries substantial risk of metastases to lymph nodes, brain, bones, liver, or lungs, which accounts for poor survival outcomes. Nonspecific characteristics of MCC increase the difficulty of differential diagnosis and can lead to diagnostic and treatment delays, even misdiagnosis. Encouragingly, growing understanding of MCC clinicopathology, epidemiology and immunohistochemistry, have raised clinicians' awareness about MCC; improved approaches to differential diagnosis have also facilitated the diagnostic process.

Previously, surgical procedures combined with postoperative radiotherapy were the first-line therapy option for primary or local MCC. Chemotherapy was used for advanced MCC, with transient responses in most cases and unclear overall survival-related clinical benefit. Over recent years, however, immunotherapy has heralded a new era of cancer treatment, remarkably improving treatment outcomes for patients with metastatic MCC.

Avelumab is the only immune-checkpoint inhibitor currently approved by the Taiwan Food and Drug Administration for treating metastatic MCC. In clinical trials, as described herein, avelumab demonstrated not merely a favorable safety profile, tolerable even among elderly patients, but also enormous clinical benefit in both treatment-naïve and chemotherapy-refractory patients; specifically, avelumab had high response rates as first-line treatment, and durable responses of ≥2-years and improved long-term survival rates as second- or later-line treatment.

The four case reports of Taiwanese MCC patients have conveyed a real-life picture of MCC treatment, including its manifestations, diagnostic processes, therapeutic strategies, and treatment outcomes. These four patients were aged from 75 to 82 years and had lymph node metastases. After avelumab treatment, they were likely to achieve partial response or even complete response, and tolerated avelumab well; most developed no immune-related adverse event.

Nowadays, avelumab is the standard therapeutic option for treating metastatic MCC in Taiwan. Long-term studies are ongoing, in the hope of achieving improved survival outcomes and quality of life for MCC patients.

1 前言

張文震 理事長 / 台灣免疫暨腫瘤學會

皮膚的小樑狀癌症 (trabecular carcinoma) 首度於 1972 年由 Cyril Toker 所提出[1]，並於六年後由 Tang 及 Toker 確認其腫瘤細胞表型 (phenotype) 的表現，進而假設這種皮膚小樑狀癌症是源自於默克細胞 (Merkel cell)[2]，這項假設最後藉由免疫組織化學染色分析 (immunohistochemical analysis) 獲得證實[3]。默克細胞癌 (Merkel cell carcinoma, MCC) 一詞於 1980 年由 De Wolff-Peeters 正式提出，沿用至今仍是最常用且廣為接受的名稱[4]。

默克細胞癌的發生率在過去二十年來逐年攀升。美國默克細胞癌每年病例數自 2000 至 2013 年增加了 95%，2013 年的疾病發生率達每十萬人年 0.7 例[5]。然而，在非白種人 (non-Caucasian) 族群發生默克細胞癌的相關文獻很少，也尚無亞洲國家默克細胞癌發生率的確切統計。此外，默克細胞癌是一種侵犯性的神經內分泌腫瘤，存活率差，約 25-50% 默克細胞癌的患者會發生復發，且五年的相對存活率 (relative survival rate) 或默克細胞癌特異的存活率 (MCC-specific survival rates) 約為 41-77%[6]。

默克細胞癌的治療方式包括手術、化學治療、放射治療及免疫療法，近年來核准的免疫療法藥物提供新的治療選擇，不但大幅改變了默克細胞癌的治療方式，也改善了病人的治療結果，而後續章節將會詳述相關資訊。由於默克細胞癌相當罕見且易受忽視，因此需要正確的診斷和及時有效的治療。此外，亞洲國家的默克細胞癌相關報告仍相當匱乏，因此本書希望藉由一些研究和案例，從專科醫師的角度為醫療從業人員提供更多有關默克細胞癌的資訊，從而改善默克細胞癌患者的存活率，並提高生活品質。

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2 專家觀點

2-1 皮膚科醫師的觀點

張曜宇 醫師 / 林口長庚紀念醫院

前言

默克細胞癌 (Merkel cell carcinoma, MCC) 是一種罕見的皮膚惡性腫瘤，最常發生在淺色肌膚的老年人。MCC 具有高度侵略性，在腫瘤切除後易復發或轉移至局部淋巴結。

危險因子

MCC 好發於淺色肌膚的族群，約 95% 的案例為白種人[1]，在東亞人口中則極為罕見。在 1970 至 2009 年間，來自中國 18 所癌症或皮膚科醫院的 310 萬件病理資料及病歷中，僅發現 22 件案例[2]。

MCC 常見於老年人，男性平均診斷年齡為 74 歲，女性為 76 歲[1]。免疫受到抑制的患者，如器官移植接受者、HIV 陽性者及罹患 B 細胞淋巴腫瘤者，具有較高的疾病發生率，且往往在年紀較輕時診斷出[3-5]。

臨床特徵

腫瘤好發於頭部和頸部等易受到陽光照射的區域，其次則是四肢及臀部。腫瘤外觀通常呈現粉紅色至紫色、圓頂型、堅硬、單一的結節，且生長迅速 (圖 1)；潰瘍並不少見 (圖 2)。整體而言，MCC 具有高度侵略性，並在腫瘤切除後，具有顯著局部復發的風險。

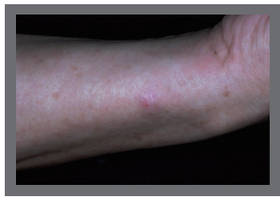

圖 1. 前臂背側有膚色至粉紅色的丘疹，有可能被誤診為良性皮膚腫瘤。

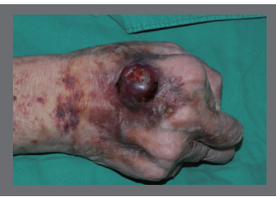

圖 2. 右手背之紅色至紫紅色、快速生長的潰瘍性腫瘤。

分析美國國家癌症資料庫 1998 至 2012 年 9,387 個 MCC 案例，診斷年齡中位數為 76 歲，其中 88% 患者年齡 >60 歲，70% 患者年齡 >70 歲。原發腫瘤最常見的部位如下 [6]：

- 頭部及頸部：43%；
- 上肢和肩部：24%；
- 下肢和臀部：15%；
- 軀幹：11%；
- 其他區域：7%。

診斷

MCC 經常被誤診為良性囊腫 (benign cyst)、脂肪瘤 (lipoma) 或化膿性肉芽腫 (pyogenic granuloma)。透過分析 27 年間診斷出一系列共 195 個案例結果，當面臨具有以下特徵的患者時，需高度懷疑 MCC 的可能性 [7]：

- 病灶無症狀或無壓痛感 (**A**symptomatic or lack of tenderness)；
- 腫塊迅速擴張 (**E**xpanding rapidly)；
- 患者處於免疫抑制狀態 (**I**mmune suppression)；
- 患者年齡 >50 歲 (**O**lder than 50 years old)；
- 腫塊發生於皮膚白皙患者且暴露於紫外線照射的區域 (**U**ltraviolet-exposed area on a person with fair-skin)。

這些特徵可以透過英文字首縮寫為 AEIOU，容易記憶。當出現其中 3 種或更多特徵時，表示 MCC 的可能性越高，必須以組織切片及組織學檢查確立診斷。

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2-2 病理科醫師的觀點

黃彥霖 醫師 / 林口長庚紀念醫院

默克細胞癌 (Merkel cell carcinoma, MCC) 是一種罕見但為高侵犯性的皮膚癌，具有神經內分泌的特性。MCC 最常見於七十多歲的白人男性，通常發生於長期曝曬的部位，如頭部、頸部，以及四肢暴露的部分。

除了長期暴露於紫外線的照射外，MCC 的發生也和默克細胞多瘤病毒 (Merkel cell polymavirus, MCPyV) 感染有關。MCPyV 陽性病人占了 MCC 案例約 80%，通常年紀比平均年齡低，同樣可能發生頭部、頸部、四肢，但有時也會發生在非曝曬部位。而 MCPyV 陰性的 MCC 較常見於頭頸部曬傷的皮膚，且伴隨其他非黑色素瘤 (non-melanoma) 之皮膚癌，如基底細胞癌 (basal cell carcinoma) 或鱗狀細胞癌 (squamous cell carcinoma) 等。部分病人出現轉移性 MCC 時，其原發病灶 (primary lesion) 可能仍未知或已經消退。

組織學上，MCC 主要發生於真皮層，但也會浸潤至皮下組織，具有清楚的邊界 (border)。MCC 癌細胞常呈實質片狀 (solid sheet)，有時也以小樑狀 (trabecular) 或類器官 (organoid) 的形式增生。雖然覆蓋在最外層的表皮層不在境界帶 (grenz zone) 內，但多達 10% 的案例因 MCC 擴及表皮層內，而難以和 Paget 氏病、Bowen 氏病或惡性黑色素瘤區別。

MCC 細胞為單形性 (monomorphic) 小型至中型的非典型 (atypical) 細胞，帶有少量的細胞質；圓形至卵形的細胞核，且因核質比 (nuclear-to-cytoplasmic ratio) 異常地高，而有相互擠壓 (nuclear molding) 的現象。細胞核之染色質呈細粒狀 (finely granular) 均勻分布 (salt-and-pepper chromatin pattern)。特殊的細胞學表現還包括細胞較為鬆散 (discohesive)，呈漿細胞樣 (plasmacytoid)，富含細胞質且透明 (clear)，或具有紡錘狀 (spindled)、未分化 (anaplastic) 的特徵。

免疫組織化學方面，MCC 細胞表現出染色顆粒素 A (chromogranin A)、突觸體素 (synaptophysin)、CD56 等神經內分泌標記，以及神經標記如神經絲蛋白 (neurofilament protein)。此外，以下表現亦可能呈陽性：B 細胞淋巴瘤 -2 蛋白 (B cell lymphoma-2, BCL-2)、CD99、CD117、CD57、p63 (罕見)、末端去氧核苷酸轉移酶 (terminal deoxynucleotidyl transferase, TdT)、磷脂肌醇蛋白聚糖 -3 (glypican-3)，以及上皮標記 (epithelial markers)，最常見的包括低分子量角蛋白 (low molecular weight keratin) CAM 5.2、上皮膜抗原 (epithelial membrane antigen, EMA)、泛細胞角蛋白抗體 (pan-cytokeratin antibody) AE1/AE3、細胞角蛋白 7 (cytokeratin 7, CK7) 及 20 (CK20)。儘管 CK20

的表現多變，但多數的 MCC 案例至少呈現局部陽性 (focally positive)，典型的表現為點狀分布 (dot-like, punctate pattern) 於細胞核旁 (paranuclear)，不過也可能在其他如細胞膜或細胞質的染色觀察到 CK20 的分布。MCC 細胞通常於波形蛋白 (vimentin)、S-100 蛋白及甲狀腺轉錄因子 -1 (thyroid transcription factor-1, TTF-1) 的表現呈現陰性。而單株抗體 CM2B4 可用於檢測 MCPyV。

鑑別診斷首先面臨的問題是如何判斷病人的 MCC 為原發性 (primary) 或轉移性 (metastatic)，例如轉移至皮膚的肺部小細胞神經內分泌癌 (small-cell neuroendocrine carcinoma of the lung, SCLC)。病人的臨床病史、組織學和免疫組織化學指標 (主要的指標包括 TTF-1、CK7 和 CK20)，可以幫助釐清。MCC 不會表現 TTF-1 和 CK7 瀰漫性免疫反應性 (diffuse immunoreactivity)，可藉此與原發性 SCLC 區分。除了 SCLC 外，其他部位的神經內分泌癌也可能轉移至皮膚，其 TTF-1 的表現也可能呈免疫陰性 (immunonegative)。要區分轉移性神經內分泌癌和 MCC，除了其他部位特異性的指標之外，最重要的是病人的臨床病史。

MCC 有以下與黑色素瘤或非黑色素瘤之皮膚癌不同的主要特徵：

1. **基底細胞癌 (basal cell carcinoma)：**MCC 缺乏柵狀周邊細胞 (palisading peripheral cells)，且呈現出神經內分泌細胞學的特性。此外，CK20 染色若呈點狀分布，很有可能是 MCC；而 MCPyV 若呈陰性，則為基底細胞癌。

2. **黑色素瘤 (melanoma)：**小細胞變異型 (small-cell variant) 需與 MCC 進行鑑別診斷，MCC 很少出現大而不規則且核仁突出 (prominent) 的細胞核；儘管有時 MCC 也能觀察到嗜黑色素細胞 (melanophage)，但出現黑色素 (melanin) 則較有可能為黑色素瘤。當 HMB-45 或其他黑色素細胞標記 (melanocytic markers) 為陰性、黑色素瘤呈 MCPyV 陰性時，免疫組織化學結果能釐清大多數 MCC 的診斷。

3. **Ewing 氏肉瘤 (Ewing sarcoma)：**Ewing 氏肉瘤是一種藍色小圓細胞腫瘤 (small-round-blue-cell tumor)，CD99 在細胞膜染色下清晰可見，而且會有 Friend 白血病融合蛋白 -1 (Friend Leukaemia Integration-1) 的細胞核染色。Ewing 氏肉瘤若發生於皮膚，能以螢光原位雜交融合技術 (fluorescence in situ hybridization) 或反轉錄聚合酶鏈鎖反應 (reverse transcription polymerase chain reaction) 檢出 t(11;22) 之染色體錯位。所有的 Ewing 氏肉瘤在免疫組織化學上均呈 MCPyV 陰性。

4. **淋巴瘤：**在形態學及免疫組織化學的表現上，淋巴瘤可能和小細胞 MCC 非常類似，兩者均可能呈現 PAX-5、TdT、CD56、CD99 陽性，因此需借助其他免疫染色法，如 CK20 和 MCPyV，才能正確診斷。

5. **皮脂腺癌 (sebaceous carcinoma)：**附屬器周邊的侵犯 (periadnexal involvement)，及類似 Paget 氏症的表皮內擴散 (pagetoid intraepidermal spread) 可能與表面 MCC (superficial MCC) 及皮脂腺癌的鑑別診斷有關。皮脂腺癌通常親脂蛋白 (adipophilin) 呈陽性，而 CK20 及 MCPyV 則呈陰性。

6. **鱗狀細胞癌：**鱗狀細胞癌若伴隨神經內分泌之分化，則無法與 MCC 區分。當 CK20 和兩個或兩個以上的神經內分泌的指標皆呈現陽性時，一般會將腫瘤判定為 MCC。

多達半數的 MCC 在進行切片檢查時，未被懷疑為 MCC，因此診斷時最重要的是保持開放的心態，認知到 MCC 也是可能的選項，並留意腫瘤的生長型態與臨床描述 (clinical description)。如果組織病理學表現與臨床懷疑不相符時，強烈建議進行更全面性的檢查，並要求臨床醫師進行更深層或切除式的切片檢查 (excisional biopsy)。皮膚癌細胞若細胞學上呈現明顯的神經內分泌的特徵，則必須評估 CK20，以及皮膚外神經內分泌癌 (extracutaneous neuroendocrine carcinomas) 的其他指標，如 TTF-1。MCPyV 的免疫組織化學檢測雖然特異度高 (specific)，卻靈敏度卻不佳 (not sensitive)，而且並非所有院所皆能執行。

病理報告應至少包含腫瘤大小、周邊及深部邊緣的狀態 (peripheral and deep margin status)、淋巴血管 (lymphovascular) 的侵犯情形，以及是否侵犯鄰近器官及組織。若病人合併鱗狀細胞癌或基底細胞癌，也應予以記錄。

檢測項目經常要求前哨淋巴結 (sentinel lymph node) 切片檢查，如果腫瘤的形態學表現不明顯，可能需 CK20 或 CAM5.2 等免疫組織化學指標來判別少量 (scattered) 的腫瘤細胞。美國癌症聯合會 (American Joint Committee on Cancer) 建議，淋巴結的報告須包括腫瘤負荷 (tumor burden)、腫瘤大小，以及是否出現淋巴結外 (extranodal) 的侵犯。

2-3 腫瘤科醫師的觀點

吳教恩 醫師 / 林口長庚紀念醫院

默克細胞癌 (Merkel cell carcinoma, MCC) 分期

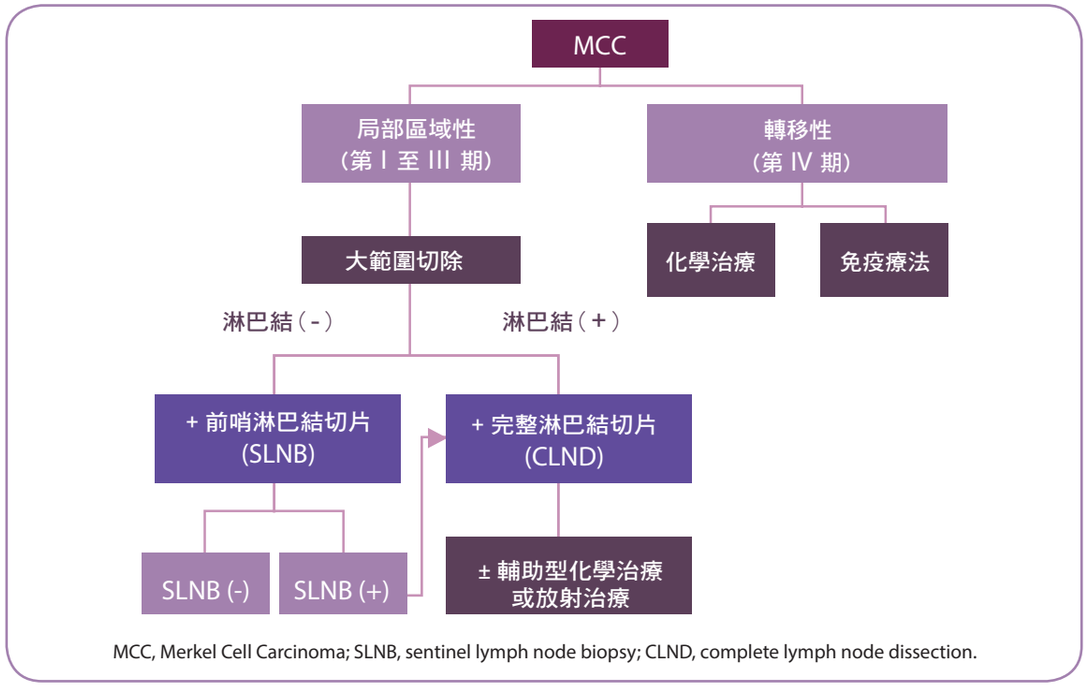
美國癌症聯合委員會 (American Joint Committee on Cancer) TNM 分期系統，依據腫瘤大小、局部淋巴結侵犯及遠端轉移情形，將 MCC 分為四期，如表 1。

表 1. MCC 分期簡表

期別	T （原發腫瘤）	N （局部淋巴結侵犯）	M （遠端轉移）
I	≤2 公分	無	無
II	>2 公分	無	無
III	不限大小	有	無
IV	不限大小	不限侵犯情形	有

治療方式

圖 1. 期別決定 MCC 治療方式



MCC, Merkel Cell Carcinoma; SLNB, sentinel lymph node biopsy; CLND, complete lymph node dissection.

◆局部區域性 MCC

局部區域性 MCC（第 1 至 3 期）患者為了達到更高的存活率，接受廣泛切除 (wide excision) 及淋巴結處置（淋巴結陰性 MCC：前哨淋巴結切片；淋巴結陽性 MCC：完整淋巴結切片）等積極的手術介入是很重要的[1]。此外，若為局部復發患者，可進行救援手術 (salvage surgery)。具有復發高風險患者則可給予輔助性放射治療或化學治療，即使輔助性治療的作用仍存在不確定性。

◆轉移性 MCC

轉移性 MCC 的初始治療，在免疫療法出現前，通常以 cisplatin 及 etoposide 的緩和性化學治療 (palliative chemotherapy) 為主，或是使用 cyclophosphamide、doxorubicin 及 vincristine 作為替代的治療選擇。但在這種情況下，化學治療的效益有限。

直到免疫療法問世以後，證實轉移性 MCC 患者對於 avelumab、pembrolizumab 及 nivolumab 等免疫檢查點抑制劑 (immune checkpoint inhibitors, ICI) 可產生持續性反應，美國食品藥物管理局 (Food and Drug Administration) 核准此三種藥物使用於 MCC。然而 avelumab 則是上述三者之中，國內目前唯一被台灣食品藥物管理署核准使用於轉移性 MCC 的 ICI，核准時間為 2018 年 8 月。

免疫檢查點抑制劑與化學治療的療效及安全性比較（過去研究）

Avelumab 用於可產生持續性反應的 MCC 患者具有良好的療效和安全性，其中包含 88 名化學治療失敗的患者（反應率：34%）[2,3] 及 39 名未曾接受過化學治療的患者（反應率：62.1%）[4]。相較於傳統化學治療，avelumab 的反應率較高，且抗腫瘤活性較持久。因此在台灣，avelumab 為轉移性 MCC 的標準治療方式。

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3 案例分享

3-1 案例 1：82 歲男性，患有大腿腫瘤和腹股溝淋巴結腫大

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案例背景

82 歲男性，具有胸腺瘤病史，25 年前接受胸腺切除手術後，以 Mestinon® (pyridostigmine) 治療。3 年前發現右大腿腫瘤，隨後腫瘤逐漸變大，尤其在過去 6 個月內特別明顯，而前往皮膚科門診就醫。患者表示沒有其他相關症狀或表徵，如發汗、食慾不振、夜間發燒或體重減輕。

診斷及處置

理學檢查發現一個約 2 公分寬、可自由移動、偏藍色的硬化腫塊；無局部壓痛或發熱，因此安排進行腫瘤完整切除手術 (en bloc resection)。

病理報告顯示為第一期、有邊緣侵犯的皮膚原發性神經內分泌癌 (pT1NxMx)。詳細檢查結果為具有高度有絲分裂活性 (高倍鏡視野下有絲分裂數超過 30 [>30/10 high-power field])、淋巴血管侵犯、cytokeratin 20 和 synaptophysin 為陽性，但 CD45、vimentin、S100、paired box gene 8、thyroid transcription factor 1、cytokeratin 7 皆為陰性。然而，患者不願意再次接受手術。

手術後兩個月，腹股溝出現腫塊。於一般外科門診進行骨盆電腦斷層掃描，檢測到右側腹股溝淋巴結腫大 (圖 1)。接受淋巴結清除術後，患者轉診進行放射線治療，治療期間再次發現右側腹股溝腫脹和腿部水腫。電腦斷層掃描顯示淋巴結腫大復發，且主動脈旁多處淋巴結腫大，伴隨下腔靜脈壓迫 (圖 2)。患者轉至癌症安寧治療。

安寧治療

詢問患者與其家屬意見，並考量患者的年齡，建議使用 avelumab，但沒有立即開始治療。由於腿部腫脹惡化，先給予經劑量調整後的 cisplatin 和 etoposide 治療。第 1 個化學治療療程後腫脹減少，但第 2 個療程後，腫脹又快速復發。此時患者行走必須使用拐杖協助，身體活動功能量表

(Eastern Cooperative Oncology Group performance status) 評分為 2 分。接著於患者的第 3 個化學治療療程中加上 avelumab，但患者出現中性球低下熱合併敗血症 (*Escherichia coli*)，因此於第 4 個療程開始僅給予 avelumab。

Avelumab 3 個療程治療後，利用電腦斷層掃描進行再分期評估，顯示有部分緩解 (partial response)，患者可以不使用拐杖行走 (圖 3)。6 個療程後再次執行再分期評估，顯示有肝臟轉移，與患者及家屬討論後，建議進行安寧照護。患者在 avelumab 最後一劑藥物給予後 2 個月死亡。投予 avelumab 的 6 個療程中，未曾發生免疫相關的不良事件。

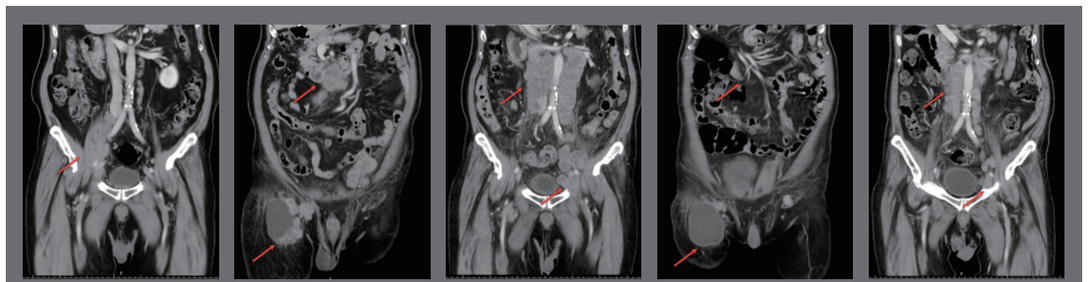


圖 1　圖 2-1　圖 2-2　圖 3-1　圖 3-2

3-2 案例 2：75 歲男性，背部復發性默克細胞癌

呂長賢 醫師 / 嘉義長庚紀念醫院

臨床表徵、診斷及治療

75 歲男性，過去曾因良性攝護腺肥大，接受攝護腺雷射手術 (laser prostatectomy)，且有慢性腎功能不全。而後發現右上背部有一處 3.5 x 3 公分進行性的紅色硬化腫塊，並有角化改變，而前往整形外科就醫及住院。病理切片診斷為侵襲性腫瘤，具有神經內分泌的特徵表現。腹部電腦斷層掃描及胸部 X 光檢查顯示無其他明顯病灶。2014 年 5 月針對背部腫瘤進行廣泛切除 (wide excision) 至邊緣無癌細胞 (free margin)。詳細病理報告顯示為 pT2 分期的默克細胞癌，伴隨原位局部表皮鱗狀細胞癌；免疫組織化學染色結果，嗜鉻粒蛋白 (chromogranin)、突觸素 (synaptophysin)、CK20、上皮膜抗原 (epithelial membrane antigen)、CD117 皆呈陽性。

患者之後未再繼續回診追蹤，直到 2017 年 2 月才因右側腋窩有進行性腫塊至急診就醫。腫塊於 1 年前開始形成，伴隨明顯的右臂淋巴水腫和麻木感。病理切片結果顯示為轉移性默克細胞癌，CK20 的免疫組織化學染色呈現陽性且細胞核旁有點狀表現 (paranuclear dot-like pattern)。電腦斷層掃描發現右腋下方有無法切除的腫塊，伴隨胸廓侵犯和血管包裹 (vessel encasement)，但無遠端轉移 (圖 1)。

由於患者年邁虛弱，給予每週 1 次含鉑的化學治療及放射治療 (5,500 cGy/20 fractions) 以控制局部病情發展，但腫瘤消退效果有限。2017 年 5 月至 9 月間，進一步合併使用鉑類及 etoposide 進行 6 個療程的化學治療，雖然腫瘤明顯消退，但右臂淋巴水腫和麻木感仍持續發生 (圖 2)。後續給予 1 週的口服 etoposide 作為維持治療，然而患者發生全身性皮膚搔癢，無法耐受藥物。

患者於 2018 年時納入全球 avelumab 早期試用計畫，自 5 月 8 日開始接受每 2 週 1 次的 avelumab 治療，結果耐受良好，右臂淋巴水腫在 2 個療程後消退。未發生免疫治療相關的不良事件 (adverse event) 或明顯副作用，僅有輕度白血球增加，連續影像學追蹤檢查顯示疾病已穩定 (圖 3)。患者仍持續接受 avelumab 治療。

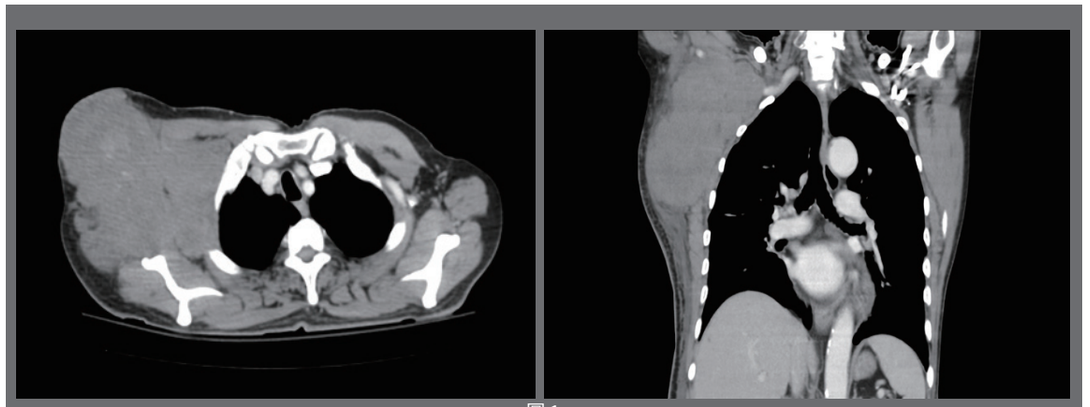


圖 1

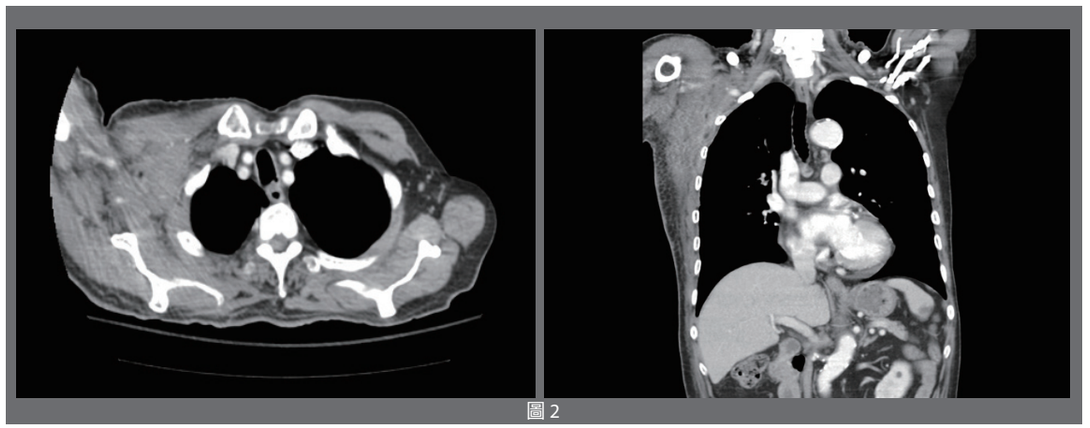


圖 2

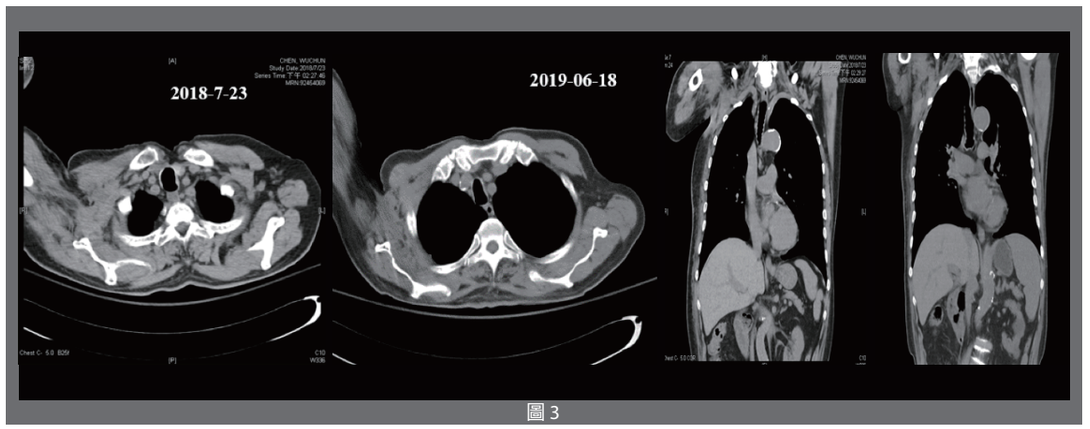


圖 3

3-3 案例 3：75 歲男性，右側小腿水腫

蔡瑞鴻 醫師 / 國立成功大學醫學院附設醫院

案例背景

75 歲男性，因冠狀動脈疾病，曾接受冠狀動脈繞道手術及心臟節律器植入。患者也有第二型糖尿病、高血壓及第三期慢性腎臟病 (血清肌酸酐 1.6 mg/dL) 等疾病。患者最初的症狀為右小腿水腫持續 2 週未消退，入院時發現右腹股溝腫塊。一開始診斷為蜂窩性組織炎，接受相關治療但未獲得改善，因此進一步進行詳細檢查。

診斷流程

下肢彩色複合式超音波 (color duplex ultrasound) 顯示，腹股溝有一個 10 x 7 公分腫塊，切片檢查後發現為小細胞癌 (表 1)。此外，全身性電腦斷層掃描、胃鏡及大腸鏡等檢查，排除源自肺、胃或腸道的小細胞癌；也未發現其他疑似病變。會診病理科醫師後，確診為默克細胞癌 Merkel cell carcinoma (MCC)。

表 1. 切片檢查結果

腫瘤組織細胞特性	結果
嗜鉻粒蛋白 (chromogranin) **突觸素** (synaptophysin)	**強陽性**
細胞角質蛋白 (cytokeratin) **點狀樣染色**	**陽性**
白血球共同抗原 (leukocyte common antigen) **甲狀腺轉錄因子** 1 (thyroid transcription factor 1)	**陰性**

治療

2017 年 3 月確診後，以 6,900 cGy/30 fractions 進行局部放射治療，同時合併 etoposide/carboplatin 全身性化學治療 (放射治療期間給予 1 個週期，結束後另外給予 3 個週期)。4 個週期的化學治療後，腫瘤達到部分反應；但由於患者發生血球減少 (cytopenia) 及無法耐受的不良事件，因而暫停化學治療。患者 MCC 病情維持穩定 1 年後，疾病開始惡化，便再次嘗試給予 etoposide/carboplatin 治療，但效果有限。2018 年 10 月，利用「恩慈使用 (compassionate use)」的方式申請 avelumab 使用。Avelumab 單一治療 6 個週期後，初始反應為疾病持續穩定。然而，患者腿部水腫又再次惡化，因此於 2018 年 12 月時，增加口服 topotecan 治療；雖因而發生第 3 級貧血及嗜中性白血球低下症 (neutropenia) 等不良事件，但之後腫瘤大小逐漸減小，腿部水腫情形也逐漸消退。

現況

患者持續接受每 2 週 1 次的 avelumab 10 mg/kg 治療，及每週期口服 4 天 topotecan 1 mg/day (截至 2019 年 6 月已治療 18 個週期，且目前仍持續接受治療)。治療過程中發生的不良事件包括第 3 級貧血，需每月進行輸血；第 2 級嗜中性白血球低下症，不需給予 G-CSF；以及第 1 級血小板低下 (thrombocytopenia) 和噁心。與免疫相關的不良事件則為第 2 級皮膚紅疹，需要給予全身性抗組織胺 (systemic antihistamine) 及局部類固醇治療。

3-4 案例 4：78 歲男性，左大腿默克細胞癌復發

蘇祐立 醫師 / 高雄長庚紀念醫院

患者背景

78 歲男性，2015 年時，因數月前左腳後跟出現一明顯且逐漸腫大的腫塊，而前往整形外科就醫；患者表示過去的狀況良好，無明顯疾病 (no appreciable disease)。腳跟的腫塊為 5-6 公分寬、外突的硬塊 (圖 1)，經由皮膚切片確認為默克細胞癌 (Merkel cell carcinoma, MCC)。電腦斷層掃描 (computed tomography) 發現左鼠蹊部及骨盆腔明顯的淋巴結腫大 (圖 2)。

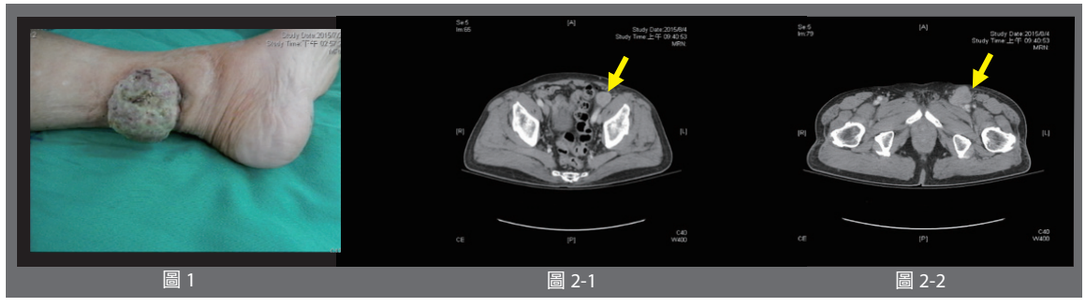


圖 1　圖 2-1　圖 2-2

隨後於 2015 年 8 月，進行左腳跟腫瘤廣泛切除、鼠蹊部及骨盆腔淋巴結切除，以及後大腿內側游離皮瓣移植手術 (free posteromedial thigh flaps transplantation)。術後病理報告證實原發腫瘤超過 5 公分 (T3) 且轉移至骨盆腔淋巴結，臨床分期為 pT3N1M1，屬於第四期癌症 (stage IV)。病患術後傷口復原良好，因而針對原腫瘤及淋巴轉移部位進行放射治療，劑量為 4,000 cGY/20 fractions。

臨床表現及診斷過程

放射治療後，患者維持無疾病的狀態，直到 2018 年 8 月回診時，左大腿皮膚表面出現許多大小不一的紅色腫塊 (圖 3)。經由皮膚切片證實為 MCC 復發。顯微鏡下觀察到小而圓的癌細胞，其免疫組織化學染色結果，CK20、CD56、synaptophysin 及 chromogranin A 呈現陽性。骨盆腔電腦斷層掃描沒有發現轉移至其他內臟。

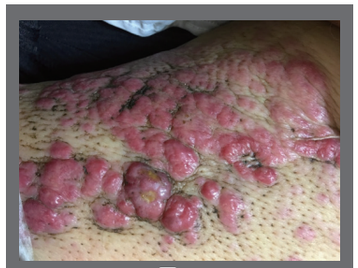


圖 3

治療

患者以 etoposide 每日 100 mg 口服 3 天，及每 3 週注射 cisplatin 50 mg/m^2 的方式治療，同時申請 avelumab 使用。化學治療進行 2 個週期後，皮膚腫瘤開始消退 (圖 4-1)，再給予 2 個週期的治療後，治療藥物轉換為 avelumab。患者對於 avelumab 治療反應良好，3 個週期的治療過程中，腫瘤持續消退。最後一次回診時，患處已無明顯病灶 (圖 4-2)，臨床判斷屬於腫瘤完全消失 (complete response)。

化學治療過程中，除貧血外，無其他血液相關的不良事件發生，但患者曾抱怨疲倦及食慾不佳。而對於 avelumab 治療，患者耐受性良好，無不良事件發生。

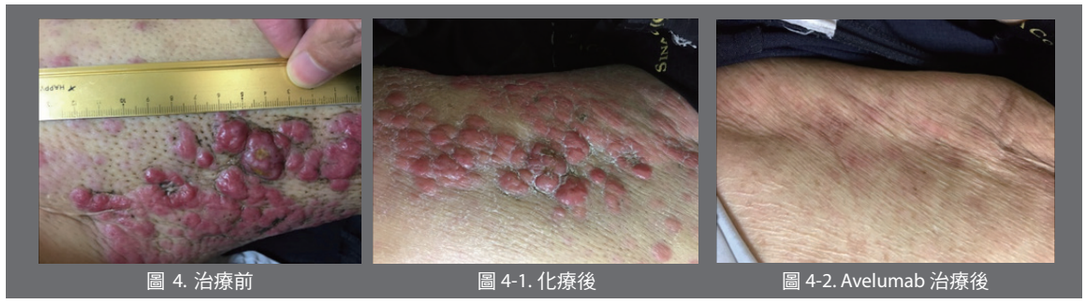


圖 4. 治療前　圖 4-1. 化療後　圖 4-2. Avelumab 治療後

患者後續狀況

患者家庭無法支持後續醫院照護問題，所以將患者轉入安養中心且中斷 avelumab 的治療。而在安養中心接受照護時，因嗆到造成吸入性肺炎；送醫時，已發生呼吸困難。家屬簽署「不接受施行心肺復甦術 (do-not-resuscitate agreement)」，後續未進行積極性治療，患者於 2 天後死亡。

4 新的治療方式—百穩益 ® 注射劑

吳教恩 醫師 / 林口長庚紀念醫院

百穩益 ® BAVENCIO® (avelumab) 介紹

Avelumab 是一種全人類單株抗體的免疫檢查點抑制劑，抑制免疫調節細胞表面配體蛋白質 programmed death-ligand 1 (PD-L1) 與 programmed death-1 (PD-1) 之間的交互作用，但不會阻斷 programmed death-ligand 2 (PD-L2) 與 PD-1 之間的作用。而在默克細胞癌 (Merkel cell carcinoma, MCC) 的細胞以及附近的浸潤性免疫細胞中，曾觀察到 PD-L1 的表現 [1,2]，因此在台灣自 2018 年起，avelumab 被核准可單獨使用治療成人轉移性默克細胞癌 [2,3]。Avelumab 的建議劑量為 10 mg/kg，每兩週一次，每次以靜脈輸注 60 分鐘的方式給予 [2]。

JAVELIN Merkel 200 試驗：A、B 部分

JAVELIN Merkel 200 為多中心、單臂、開放性的第二期臨床試驗。納入年齡 ≥18 歲、組織學確診為轉移性默克細胞癌的患者，不論 PD-L1 的表現及默克細胞多瘤病毒 (Merkel cell polyomavirus) 的狀態為何。受試者以每兩週一次 10 mg/kg 的劑量接受 avelumab 靜脈注射，直到退出試驗、出現無法耐受的不良反應或疾病惡化。試驗以不同次族群區分為：88 名患者曾於轉移疾病時接受化學治療 (A 部分) 及 39 名未曾接受過全身性治療 (B 部分)。

A 部分—曾接受治療的患者 [2]

A 部分的主要療效指標為確認的最佳整體反應 (confirmed best overall response)，定義為完全反應 (complete response)、部分反應 (partial response)、疾病穩定 (stable disease) 或疾病惡化。共計 88 名患者的年齡中位數為 72.5 歲且都接受過至少一項遠端轉移治療。有 28 名 (31.8%) 達到客觀反應 (objective response)，包括 8 名完全反應、20 名部分反應，另有 9 名患者達到疾病穩定狀態。62 名 (70%) 發生與治療相關不良事件，主要是 1-2 級不良事件；4 名病人發生 5 件 3 級不良事件，但沒有人發生 4 級或更嚴重、與治療相關的不良事件。這些結果顯示，對於化療治療失敗的轉移性默克細胞癌患者，即使是老年人，avelumab 也有效且耐受性良好。

A 部分——長期追蹤

在另一個追蹤中位數達 16.4 個月的分析中 [4]，客觀反應率為 33.0%，其中 10 名患者達完全反應、19 名達部分反應。無惡化存活期及整體存活期的中位數分別為 2.7 個月及 12.9 個月；1 年無惡化存活率及整體存活率為 30% 及 52%。這些令人鼓舞的研究結果顯示，avelumab 可能為化療後發生轉移性默克細胞癌惡化的患者帶來潛在的長期益處。

而兩年以上追蹤期的新療效資料顯示 [5]，無惡化存活率仍維持穩定的狀態：1 年 29%、18 個月 29% 及 2 年 26% (圖 1)；而中位數整體存活期為 12.6 個月，2 年整體存活率為 36% (圖 2)。這些結果證實 avelumab 在轉移性默克細胞癌患者中，具有持續持久反應和有意義的存活結果。

圖 1. 使用 avelumab 治療默克細胞癌的無惡化存活期曲線

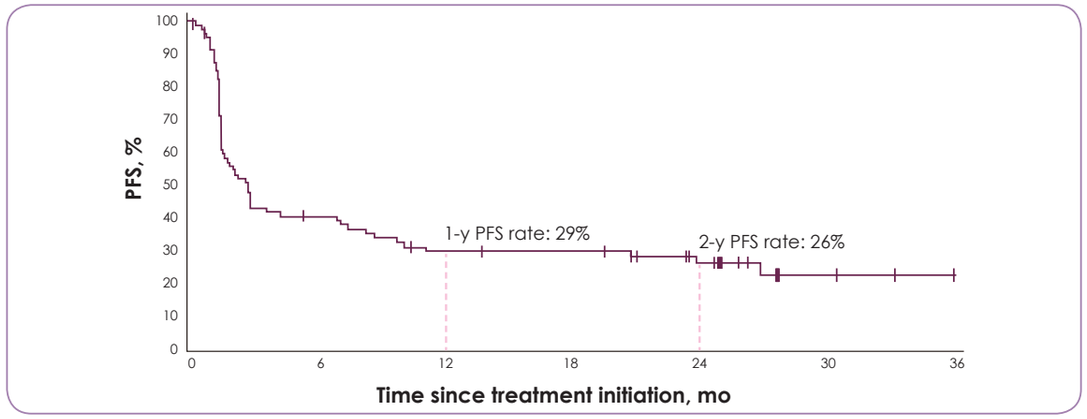
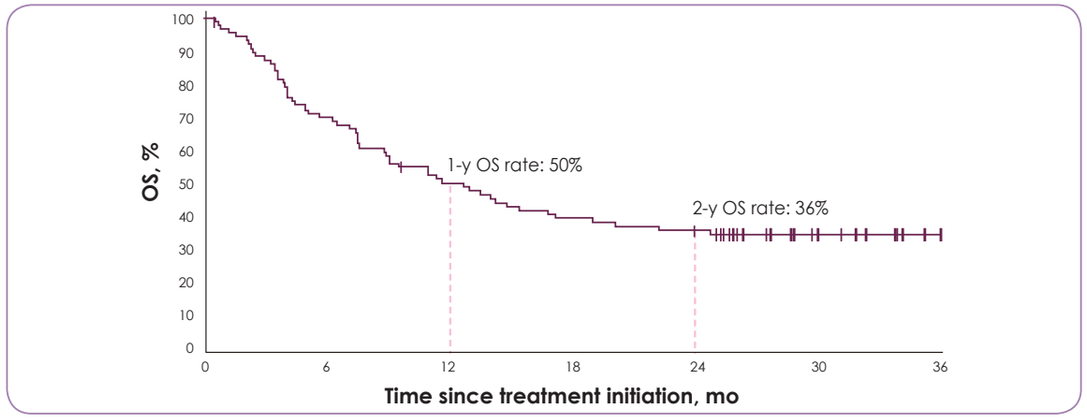


圖 2. 使用 avelumab 治療默克細胞癌的整體存活期曲線



B 部分——未曾接受治療的病患 [6]

JAVELIN Merkel 200 納入 39 名未曾接受治療的轉移性患者，評估 avelumab 用於第一線治療的療效及安全性。主要療效指標為持久反應 (durable response)，定義為客觀反應至少持續 6 個月。患者的平均年齡為 75 歲，其中 29 名患者追蹤至少 3 個月以上；14 名追蹤至少 6 個月。18 名 (62.1%) 達到客觀反應 (4 名完全反應，14 名部分反應) 且 24 名 (83%) 患者表現持久反應。追蹤 6 個月以上的 14 名患者中，71.4% 達到客觀反應 (4 名完全反應，6 名部分反應)，89% 具有持久反應。39 名患者中，28 名 (71.8%) 發生治療相關不良事件：8 名發生 3 級不良反應，但沒有人發生 4 級或更嚴重的不良事件。以 avelumab 做為第一線治療轉移性默克細胞癌病人，具有高反應率及理想的耐受性。

表 . Avelumab 第一線及第二線治療默克細胞癌之療效摘要

	第一線治療 [6]		第二線治療 [4,5]	
追蹤期	≥3 個月 (N=29)	≥6 個月 (N=14)	≥1 年 (N=88)	≥2 年 (N=88)
客觀反應率 (%)	62.1	71.4	33.0	33.0
完全反應	13.8	28.6	11.4	11.4
部分反應	48.3	42.9	21.6	21.6
疾病穩定	10.3	7.1	10.2	10.2
疾病惡化	24.1	14.3	36.4	36.4
無法評估	3.4	7.1	20.5	20.5
反應持續時間 (月) 中位數 (95% CI) 最小值，最大值	NE (4.0-NE)	NE (4.0-NE)	NE (18.0-NE), 2.8-23.3+*	NR (18.0-NE), 2.8-31.8+*
反應持續時間 ≥6 個月 (95% CI), %	83 (46-96)	89 (43-98)	93 (74-98)	-
無惡化存活期 (月) 中位數 (95% CI)	9.1 (1.9-NE)	-	2.7 (1.4-6.9)	-
整體存活期 (月) 中位數 (95% CI)	NE	-	12.9 (7.5-NE)	12.6 (7.5-17.1)

NE, not estimable (未評估); NR, not yet reached (未達到)
* 觀察到的最大值持續反應中

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5 結 論

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默克細胞癌 (Merkel cell carcinoma, MCC) 是一種罕見的皮膚癌，具高度的侵襲性，因此容易轉移至淋巴結以及腦、骨骼、肝和肺，往往造成較差的存活結果。此外，MCC 的臨床表現不具特異性，因而導致鑑別診斷困難而費時，甚至可能造成誤診，而無法及時給予病患有效的治療。所幸目前我們對於 MCC 的病理學型態特徵，及免疫組織化學的表現，有越來越充分的認識，可提高臨床醫師對於 MCC 的警覺；鑑別診斷的方式也隨之日益進步，更可加速 MCC 的診斷時程。

過去，外科手術後給予放射治療是原發或局部 MCC 的第一線治療，而化學治療則用於治療晚期 MCC，但化學治療的反應大多是短暫的，對整體存活的相關臨床益處仍不明確。然而，近年來免疫療法開啟了癌症治療新的紀元，大幅改善了轉移性 MCC 病患的治療成果。

Avelumab 是目前臺灣衛生福利部食品藥物管理署唯一核准用於治療轉移性 MCC 的免疫檢查點抑制劑。誠如前面章節所述，由臨床試驗結果可見，即便使用於老年族群，avelumab 也具有良好的安全性；在治療成效方面，avelumab 不只用於第一線治療能展現卓越的緩解率 (response rate)，用於後線治療也顯示其療效能持續長達兩年以上，而有助於維持病人長期的存活率。

而前述四例臺灣的案例報告，呈現了 MCC 案例的症狀表現、診斷過程、治療方式及結果。這四位病患年齡介於 75 至 82 歲，腫瘤大多發生淋巴轉移。經 avelumab 治療後，可達到部分緩解 (partial response) 甚至完全緩解 (complete response)；均可耐受 avelumab，且大多未發生免疫相關之不良反應。

Avelumab 是台灣目前轉移性 MCC 的標準治療方式，後續長期研究仍在持續當中，以期能使 MCC 病患達到更佳的存活結果，並改善生活品質。

Merkel Cell carcinoma 默克細胞癌—
Overview, Specialists' Perspectives and Case Reports〖中英對照〗

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