Merkel cell carcinoma is a rare cutaneous undifferentiated carcinoma. The optimal management of Merkel cell carcinoma has not been clearly defined. We report a patient, who was a 74-year-old man with a 4 × 4 cm reddish nodule at left thigh. Skin biopsy was performed and the diagnosis of Merkel cell carcinoma was made by electron microscopic and immunohistochemical examination. Then, wide local excision and split thickness skin graft was performed. The magnetic resonance imaging demonstrated residual tumor. Radiation therapy to the left thigh and ipsilateral inguinal area was instituted two months after surgery. We review the electron microscopic and immunohistochemical findings and also describe the effect of radiation therapy for this case.

Key words: Merkel cell carcinoma; Cutaneous undifferentiated carcinoma

Merkel cell carcinoma (MCC) is a very rare primary skin cancer. Toker firstly described it in 1972 as "trabecular carcinoma of the skin" [1] and high incidence of recurrence and metastasis had been observed [2]. Only four cases have been reported in Taiwan [3,5].

Various designations have been used for Merkel cell carcinoma in the literature, including neuroendocrine carcinoma of skin, primary small cell carcinoma of skin, and Merkel cell tumor. Because the structure of the tumor cell is strikingly similar to that of the Merkel cells, which are found in the basal layer of epidermis, it is believed that this tumor derives from the Merkel cells. The tumor can be properly diagnosed microscopically by immunoperoxidase stains.

Due to its aggressiveness and unfavorable prognosis, prompt diagnosis and adequate treatment are essential. Wide local excision with adequate margins followed by radiation therapy is the treatment of choice. However, there are still some arguments in the role of systemic chemotherpy [4].

CASE REPORT

A 74-year-old man visited our dermatology clinic on November 20, 1999. He had a rapidly growing 4 × 4 cm erythematous tumor with central erosion (Fig 1) on his left thigh for two months. No inguinal lymphadenopathy or other abnormalities were noted on physical examination. Laboratory data revealed normal hepatic and renal function, except for high uric acid level, which was 10.6 mg/dl. ACTH and tumor markers including CEA, PSA, Alpha-fetoprotein, SCC and tissue polypeptide antigen (TPA) were all within the reference ranges. Chest PA and lateral views showed no evidence of cardiopulmonary disease.

The lesion was removed by excisional biopsy under local anesthesia on December 31, 1999. Hematoxylin and eosin (H&E)-stained tissue showed a dermal malignant neoplastic proliferation that slightly infiltrated the subcutaneous fat tissue. Immunohistochemical studies showed both epithelial and neuroendocrine characteristics. Under electron microscopic
examination, the paranuclear dense-core membrane-bound secretory granules were noted (Fig 2). This finding was consistent with MCC. Wide excision with the Mohs’ microsurgery and meshed split thickness skin graft (donor site at patient’s right thigh) were performed on January 20, 2000.

The pathology study revealed multinodular / lobular growth of solid tumor nests in the dermis layer, abutting the subcutaneous fat. Apparent Grenz zone separates the tumor from the overlying epidermis. The neoplastic cells are rather monomorphic, composed of round amphophilic cells with homogeneous nuclei and scanty cytoplasm (Fig 3). The chromatin pattern is finely granular and dusty. Rare spotty necrotic foci are noted. Several immunoperoxidase stains were performed which showed positive reaction to neuron-specific enolase (NSE), chromogranin, and low molecular-weight cytokeratin. Additional PAP immunostaining of Vimentin, HMB-45 and S-100 protein was performed and the above antibodies fail to decorate the neoplastic cells, thus the possibility of cutaneous melanoma was excluded. The tumor cells also showed dot-like staining with antibodies to low molecular weight cytokeratin, which was characteristic for Merkel cell (Fig 4).

Further survey including the abdominal sonography and brain computed tomography revealed no evidence of tumor metastasis. Ga-67 tumor whole body scan showed increased activity over left proximal thigh and right middle thigh, while Tc-99m sulfur-colloid lymphatic scintigraphy showed relatively delayed left inguinal lymph nodes uptake.

The magnetic resonance (MR) images demon-

Figure 1. One 4 × 4 cm erythematous tumor with central erosion over the left thigh.

Figure 2. Electron microscopic examination showing the paranuclear dense-core membrane-bound secretory granules.

Figure 3. Histological photomicrography showing the neoplastic cells are rather monomorphic, composed of round, amphophilic cells with homogeneous nuclei and scanty cytoplasm. (H&E; × 400)

Figure 4. Histological photomicrography showing the tumor cells with dot-like staining with antibodies to low molecular weight cytokeratin. (Immunoperoxidase stain; × 400)
Merkel cell carcinoma demonstrated a skin defect over the anterior aspect of the left thigh. Residual soft tissue plaque with intermediate T1-signal intensity, intermediate T2-signal intensity and significant enhancement was also noted at the lesion site. Residual tumor was suspected, while no lymphadenopathy was identified.

Patient was referred for adjuvant radiotherapy (RT) two months after surgery. A total dose of 5800 cGy via the 6 MeV electron beam was given by applying cone-down technique with one piece of 1 cm bolus put above the skin of the surgical bed. Subcutaneous 0.5 cm was included in the range of 90% isodose curve, subcutaneous 1 cm in the range of 80%, subcutaneous 1.5 cm in the range of 40% and subcutaneous 2 cm in the range of less than 30%. The fraction schema was 200 cGy/ fraction, 1 fraction per day and 5 days per week. The initial field encompassed the surgical bed with 10 cm margins and left inguinal lymphatic area. The margins of the surgical bed were then sequentially reduced to 5 cm at the dose of 4200 cGy. The treatment course had been interrupted at 4200 cGy/ 22 fractions due to irradiation dermatitis with moist desquamation. After supportive treatment for two weeks, the radiation course was completed.

During the monthly follow up course after radiotherapy, the left leg showed good functional reserve. MR images of left thigh revealed no evidence of residual or recurrent tumor at the primary tumor site two years after radiotherapy (Fig 5a and 5b). No evidence of sentinel or distant lymph node metastasis or distant metastasis was noted more than two years after operation.

DISCUSSION

Merkel cell carcinoma (MCC) is an aggressive primary cutaneous neoplasm. The cell of origin is thought to be a pluripotential cell that may differentiate in a neuroendocrine direction, as evidenced by the typical membrane-bound neurosecretory granules seen within the neoplastic cells by electron microscopy. The tumor can be easily confused with metastatic small cell carcinoma of bronchogenic origin, metastatic neuroblastoma, malignant lymphoma, malignant melanoma, metastatic atypical carcinoid and undifferentiated carcinoma of skin appendages [5]. Immunoperoxidase stains are helpful in distinguishing MCC from other tumors. Typical dot-like staining with antibodies to low molecular-weight cytokeratin is characteristic [6], which is usually absent in small cell carcinoma of lung or other organs [7]. Cytoplasmic reactivity for NSE, chromogranin and negative staining for S-100 and HMB-45 are also helpful.

MCC mainly occurs in the elderly patients and involves predominantly the sun-exposed areas. Raaf et al stated that 44% of the eruptions occurred in the head and neck, 28% in the legs and 16% in the arms. The incidence of regional lymph node spreading is 45 to 90% in their study and that of distant metastasis is 18 to 52% [8-10]. MCC has a very unfavorable prognosis. Hitchcock et al have estimated a three-year survival rate of 55% and about one-third of patients develop local recurrence within one year of excision [11]. Depending on the stage of the tumor, several therapeutic strategies including surgery, radiotherapy and chemotherapy may be adopted [12,13].

![Figure 5a](image1.png) ![Figure 5b](image2.png)

**Figure 5.** MR images of left thigh revealed no evidence of residual or recurrent tumor in the primary tumor site two years after radiotherapy. a. Axial unenhanced T2-weighted MRI (TR:1600ms, TE:90ms, ECHO:2/2) b. Coronal unenhanced STIR MRI (TR:1500ms, TE:100ms, ECHO:1/1).
Merkel cell carcinoma

Recent data according to a study with large patient number have shown an unpredictable biologic behavior of MCC, and thus an aggressive therapeutic approach at the time of diagnosis is required [14]. The primary lesion is usually widely excised with or without regional lymph node dissection [11], while the satellite regional tumors can be treated with surgery, radiation therapy or both. For patients in advanced stages of the disease, chemotherapy has gained partial success. Only a small percentage of the patients achieve complete remission, while most experience only temporary palliation [12].

Local and regional treatment for all stages of MCC is currently recommended. Adjuvant radiation therapy followed by wide excision has been reported to achieve higher local control rate and survival rate as compared with wide excision alone. Although not yet been clearly delineated in the literature, wide local excision with a margin of 2.5 to 3 cm followed by radiation in doses of 5000 to 6000 cGy over four to six weeks in 20 to 25 fractions had been recommended as the standard protocol for the treatment of the primary lesion [15].

A retrospective review of 33 patients at the Massachusetts General Hospital was reported, in which 22 primary tumors were without metastasis, 8 tumors with additional lymph node metastasis and 1 with distant metastasis. Eight of these patients underwent local excision with or without radiotherapy. Four patients with lesions in head and neck region received radiotherapy alone. Fifteen patients developed recurrences (7 local, 8 nodal, and 10 distant) during their follow-up course with the median time of 8 month from onset to recurrence. Of the 7 patients with tumor-related deaths, six had their lesions at truncal location (P< 0.001). Locoregional recurrences did not occur in patients with their safty margins of resection no less than 2 cm or in those with adequate radiotherapy [16]. Another study from Concord Repatriation General Hospital reported 33 patients with MCC. The average age of patients was 80 years. Fifty-three percent of the tumors were located in the head and neck region. Twenty-seven patients developed metastatic disease with the average time interval of 13.4 months from the first presentation to metastasis. The incidence of locoregional recurrence was 42%. Radiation combined with surgery achieved locoregional control in 15 of the 19 patients with primary, regional or recurrent locoregional disease. They suggested the local excision combined with regional lymph node clearance and adjuvant radiation treatment may improve the survival rate. The role of chemotherapy remains unclear [17]. Twenty-two patients were identified from the 6 hospitals of the Scripps Health facilities. Eight patients underwent Mohs’ surgery with permanent tissue technique. None of these patients had a subsequent local recurrence. Six patients received adjuvant radiation therapy, only one of them developed recurrence within a radiation port. Systemic chemotherapy was given to seven patients. They concluded that Mohs’ surgical technique combined with radiation therapy provides excellent local control. Systemic treatment is associated with high response rates, but to the authors’ knowledge durable responses are uncommon [18].

With respect to our experience, a local control can be achieved with an immediate postoperative radiotherapy for the primary tumor site and the adjacent lymph nodes.

REFERENCES

3. 黃輝媚，謝惠美，李玉雲。 Merkel細胞癌：3病例報告。臺灣醫學會 1991; 90: 900-903
Merkel細胞癌：一病例報告

黃世儀1 連煒隆1 張家綺2 湯人仰1 黃志仁1 何耀輝1

高雄醫學大學附設醫院 放射腫瘤部1 皮膚科2

Merkel細胞癌是一種少見的皮膚未分化癌，對於此疾病的治療仍未定論。本篇報告一位七十四歲男性病患在左大腿發現一處直徑約四公分的紅色結節。病人接受皮膚切片並利用顯微鏡與免疫組織化學檢查診斷出是Merkel細胞癌。於是施行大範圍局部切除和薄皮厚度皮膚移植。術後左大腿的核磁共振影像檢查結果疑似有局部殘存腫瘤，故轉介到本科接受左大腿與同側腹股溝淋巴區域的放射線治療。本文除檢討顯微鏡與免疫組織化學檢查之結果，另也描述病人接受放射線治療後的反應。

關鍵詞：Merkel細胞癌；皮膚未分化癌；放射線治療