Merkel Cell Carcinoma

Shravan Shanbhag¹ · Amol Amonkar¹

Received: 17 November 2015 / Accepted: 31 January 2017 / Published online: 12 February 2017
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Abstract Merkel cell carcinoma is a primary neuroendocrine tumour of the skin arising from the dermis and extending into the subcutis, occurring commonly in sun-exposed areas of the head and neck of the elderly. Clinically, non-specific erythematous or violaceous firm nodules or small plaques which may be surrounded by small adjacent satellite tumours are seen. Diagnosis of Merkel cell carcinoma is difficult by light microscopy alone and need of ancillary techniques like electron microscopy and immunohistochemistry may be necessary. Treatment modalities are dependent on the stage of the disease. We report a 73-year-old male who presented with multiple nodular swellings on the right buttock, right side of the lower abdomen, and right upper thigh since 2 months. Biopsy revealed Merkel cell carcinoma and immunohistochemistry confirmed it. In order to stage the disease, an ultrasound abdomen was done which showed multiple enlarged para-aortic lymph nodes and retroperitoneal lymph nodes with necrotic centres and right-sided hydronephrosis and computed tomography is advised for further co-relation. Computed tomography of the abdomen showed extensive lymphadenopathy with perinodal fat forming conglomerate masses in the para-aortic, aortocaval, retrocaval, bilateral iliac, and inguinal region encasing the aorta, vena cava, and bilateral iliac arteries; extensive soft tissue density nodules in the skin extending into the subcutaneous plane and superficial muscular plane of the gluteal region and lower abdomen; and mild hydronephrosis of the right kidney due to encasement of lower ureter by lymphadenopathy. We report a case of

Merkel cell carcinoma with distant metastases with the same relevant discussion.

Keywords Primary neuroendocrine carcinoma of skin · Merkel cell carcinoma · Microscopy · Immunohistochemistry · Skin

Abbreviations

MCC Merkel cell carcinoma
SCLC Small cell lung cancer

Introduction

Merkel cell carcinoma (MCC) was first described by Toker in 1972 [1, 2]. It is an uncommon cutaneous tumour that mainly occurs in sun-exposed skin of the head and neck areas of the elderly [1, 3]. This tumour is also known as primary neuroendocrine tumour of the skin or trabecular carcinoma of the skin [1, 2]. Controversy over its precise cause underlies the variety of designations to this tumour; cytological and immunohistochemical studies have shown that cells of MCC have both epithelial and neuroendocrine characteristics. It is generally believed that both normal Merkel cells and malignant Merkel cells arise from the epithelial tissue and acquire neuroendocrine features such as neurosecretory granules [1]. Clinically, it presents as non-specific erythematous or violaceous firm nodules or small plaques which may be surrounded by small adjacent satellite tumours [1, 4, 5]. We report a case of MCC presenting multiple nodular swellings on the right buttock, right side of the lower abdomen, and right upper thigh. To the best of our knowledge, Merkel cell carcinoma is a rare entity and the management of MCC is controversial owing to its rarity and lack of randomized trials. In our case report, we present a case of Merkel cell carcinoma with distant metastases.

✉ Amol Amonkar
amonkaramol@gmail.com

¹ Department of Surgery, K.S Hegde Medical Academy, Mangalore, India

Case Report

We report a 73-year-old male who presented with multiple nodular swellings on the right buttock, right side of the lower abdomen, and right upper thigh since 2 months associated with scrotal swelling and penile swelling since 1 month. Initially, the patient noticed the swelling over the right buttocks which was initially the size of a single pea and gradually grew in size over a period of 2 weeks; multiple small satellite swellings developed around the main lesion. Over the next 2 weeks, multiple nodular swellings developed on the right side of the lower abdomen and right thigh and gradually increased in size, not associated with pain, itching, malaise, loss of appetite, or cachexia. On general physical examination, a non-pitting oedema was noted over the right buttock, right thigh, and right side of the lower abdomen; pitting type of oedema was noted over the penis and the scrotum. Lymph nodes could not be palpated due to skin thickening. On local examination, multiple erythematous to waxy nodules of varying sizes were seen in groups on the right lower abdomen, right thigh, and right buttock (Fig. 1). A central large nodule with multiple satellite lesions over the right buttocks, firm to hard in consistency. Few nodules were ulcerated with crusting and erythema, and induration of the surrounding skin was noted. A non-pitting type of oedema over the right buttocks was noted. A *peau d' orange* appearance was noted on the right side of the lower abdomen. Scrotal and penile oedema was present. Biopsy from the lesion of the right buttock, right thigh, and right side of the lower abdomen revealed Merkel cell carcinoma. Ultrasound abdomen showed multiple large para-aortic lymph nodes and retroperitoneal lymph nodes, largest measuring 3 cm with necrotic centres and right side hydronephrosis, advised contrast enhanced computed tomography (CECT) for further co-relation. CECT of the

Fig. 1 **a** Multiple erythematous to waxy nodules of varying sizes with a large central lesions surrounded by multiple small satellite lesions with few nodules showing crusting and ulceration on the right side of the lower abdomen and right thigh associated with scrotal and penile oedema; the surrounding skin is erythematous with characteristic *peau d' orange* noted. **b** A large central nodule surrounded by multiple small satellite lesions on the right buttock

abdomen and pelvis revealed extensive lymphadenopathy with perinodal fat forming conglomerate masses in the para-aortic, aortocaval, retrocaval, bilateral iliac, and inguinal region encasing the aorta, vena cava, and bilateral iliac arteries. Extensive soft tissue density nodules in the skin extending into subcutaneous plane and superficial muscular plane of the gluteal region and lower abdomen and mild hydronephrosis of the right kidney due to encasement of lower ureter by lymphadenopathy were also noted on computed tomography (Fig. 2). Chest x-ray showed a right-sided pleural effusion; immunohistochemistry markers confirmed Merkel cell carcinoma. The final diagnosis of Merkel cell carcinoma stage 4 (distant disease) was made. An oncology opinion was sort and palliative care with or without chemotherapy and radiation therapy was advised. The patient expired during the course of palliative care. We report a case of MCC stage 4 with distant metastasis carrying a very grim prognosis.

Discussion

Merkel cell carcinoma or primary neuroendocrine tumour of the skin is a relatively recently described tumour which was coined by Cyril Toker in 1972 [1]. Subsequent ultrastructural examination of these tumours showed dense core granule characteristic of Merkel cells; however, discrepancy between the location of the tumour still exists. Immunohistochemistry has further established Merkel cell origin. Merkel cells are derived from asymmetric cell division of basilar keratinocytes and are found as early as the eighth fetal week [3–5]. Normal Merkel cells are found in the basal epidermis as well as in the papillary dermis as collections around sensory nerves known as “touch domes” or *haarsheiben*. Merkel cells function as mechanoreceptors releasing glutamate to juxtaposed sensory nerves in response to pressure stimulation [2, 3]. The epidemiology is loosely defined as only a few case series and reviews are reported; however, the important risk factors are increasing age and fair skin type [1, 2]. Males are showing a greater preponderance [1]. Clinically, MCC presents a non-specific erythematous or violaceous firm nodule which is surrounded by multiple satellite lesions as it did in our case. Most commonly involving periorbital areas of older adults and sun-exposed areas of elderly [1, 3]. Our case is an exception as it presented at atypical sites that is not described in the literature. Tumours less than 2 cm are asymptomatic at presentation but advanced stage tumours are large, painful, and ulcerative [1]. MCC is often misdiagnosed as a basal cell carcinoma, amelanotic melanoma, and cutaneous lymphoma; hence, a careful and complete skin and lymphatic examination to establish tumour spread is mandatory [1]. In our case, it was not possible for lymph node examination because of the skin thickening giving a woody feel on palpation; hence, underlying lymph nodes were unable to be clinically palpated.

Fig. 2 **a** Computed tomography (CT) scan showing skin nodules over the right side of the lower abdomen and gluteal region extending to the subcutaneous plane and superficial muscular plane. **b** Computed tomography (CT) scan showing mild hydronephrosis of the right

kidney due to encasement of lower ureter by lymphadenopathy and extensive lymphadenopathy with perinodal fat stranding forming a conglomerate masses in the bilateral iliac and inguinal region, encasing the aorta, vena cava, and iliac arteries

Radiologically, imaging using chest x-ray and CT scan is necessary to determine the stage and rule out the possibility of small cell variant of lung cancer. MCC has a tendency to invade dermal lymphatics early in disease progression [1]. Metastases eventually occur in 50% of all MCC patients, most commonly to the skin, lymph nodes, liver, bone, lung, and brain. On histology, MCC shows sheets of monomorphous small blue cells with diameters up to 15 μm [1]. These tumours may be confused histologically with other small blue cell tumours like SCLC of bronchial origin, cutaneous lymphoma, neuroblastoma, or Ewings sarcoma (Fig. 3). Immunohistochemistry markers like cytokeratin 20 (CK 20), epithelial membrane antigen, neuron-specific enolase, and synaptophysin staining result in a characteristic peri-nuclear dot [1]. Treatment modalities are controversial and non-

uniform as they are based on retrospective analysis of small subset of patients [2]. Although there is no ideal regimen, stage-specific approach is used and divided into four stages [1]. Stage I MCC without evidence of regional or distant metastasis (localized tumour) excision of tumour to the fascia with up to 3 cm surgical margins have been reported with or without radiation therapy or sentinel lymph nodes biopsy [3]. Stage II MCC with evidence of regional lymph node spread, wide local excision plus therapeutic lymph node dissection with or without radiation therapy or chemotherapy [1]. Radiation doses greater than 5000 cGy may be required for bulky disease, and chemotherapy similar to small cell regimen with platinum-based agents like cisplatin, carboplatin, and etoposide can be given concurrently or subsequently with radiation therapy. Stage III MCC without evidence of distant

Fig. 3 **a** On microscopy (low power), dermal infiltrate of small round blue tumour cells with crush artifact is seen. **b** On microscopy (high power), dermal infiltrate of small round blue tumour cells with crush artifact is seen

metastasis revolves around surgery with or without chemotherapy or radiation therapy [1]. Chemotherapy with doxorubicin is reserved for patients with stage 4 MCC; however, it is not associated with increased survival based on the reports.

TNM Staging for Merkel Cell Carcinoma

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour size less than 2 cm
T2	Tumour size more than 2 cm but less than 5 cm
T3	Tumour size more than 5 cm
T4	Tumour has invaded adjacent tissues such as muscles, bones, or cartilage
N0	No spread to regional lymph nodes
N1a	Spread to regional lymph nodes but not detected on clinical examination or imaging
N1b	Spread to regional lymph nodes detected by clinical examination or imaging and confirmed by biopsy
N2	Spread toward a nearby lymph node area without reaching the lymph nodes (in transit metastasis)
M0	No spread to distant organs
M1a	Spread to other areas of the skin, tissues under the skin, or to distant lymph nodes
M1b	Spread to lungs
M1c	Spread to other organs
Stage 0	Tis N0 M0
Stage 1A	T1 pN0 M0
Stage 1B	T1 cN0M0
Stage 2A	T2 or T3, pN0, M0
Stage 2B	T2 or T3, cN0, M0

Stage 2C	T4 N0 M0
Stage 3A	Any T, N1a, M0
Stage 3B	Any T, N1b or N2, M0
Stage 4	Any T, Any N, M1

cN0—regional lymph nodes do not look or feel abnormal but the nodes have not been biopsied yet.

pN0—regional lymph nodes have been biopsied and no malignancy was found in them.

Conclusion

We conclude by stating Merkel cell carcinoma is a rare clinical entity and only a handful of cases are reported till date. The management of MCC is dependent on the stage of the disease and is hampered by its rarity and due to lack of randomized trials. Sentinel lymph node biopsy is helpful in staging and prognosis of the disease but its benefit on survival is yet to be seen. The prognosis of MCC is variable and successful outcomes are most often seen in patients with early diagnosis and complete excision of tumour.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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