

Diagnosis of merkel cell carcinoma at chronic venous ulcer: case report

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SUMMARY

Merkel-Cell Carcinoma (MCC) is rare and highly aggressive skin cancer, usually due to Merckel-cell polyomavirus. Venous ulcers are full-thickness defects of skin in the lower limb when these ulcers persist for more than 6 weeks; they are referred to as chronic venous ulcers. An 83-year-old male presented to Al-Sadder Teaching hospital, with a chief complaint of painful swelling of the right leg with the same side foot ulcer for one month. On examination the ulcer found in the medial aspect of the ankle, just posterior and down to the medial malleolus. Its size about 2 cm × 3 cm, with an oval shape. The edge raised and everted with whitish discoloration. The base was firm, immobile, tender, red spots floor, and whitish offensive discharge. The patient was admitted to the hospital for the correction of anemia and rehydration. Unfortunately, the patient died before chemotherapy after 6 days of final diagnosis and staging. Taking into account the frequency of cutaneous malignancies associated with Chronic Leg Ulcers (CLU); CLU presumed to be of vascular origin should be biopsied after 6 weeks to 3 months of non-healing wounds. In the present study, we report a rare case of MCC in CLU in Misan Province, Iraq.

Key words: merkel-cell carcinoma, skin cancer, venous ulcers, Misan

INTRODUCTION

Merkel-cell carcinoma is a rare, and aggressive cutaneous neuroendocrine malignancy [1]. It is characterized by a high incidence of local recurrence, regional nodes metastases, distant metastases, and high mortality [2, 3]. It is believed to arise from Merkel's cells that are neuroactive cells of neuroendocrine origin found in the stratum basale of the epidermis [4]. About 80% of MCC tumors are infected with Merkel Cell Polyomavirus (MCV) [5]. Usually, MCC presented as a firm, painless, nodule (up to 2 cm) or mass (>2 cm) [6]. Venous ulcers are full-thickness defects of skin in lower limb mostly at ankle region, due to venous hypertension, also known as a Chronic Venous Disease (CVD) of the lower limb [7] (Figures 1A and 1B). When these ulcers persist for more than 6 weeks, they called chronic Venous Leg Ulcer (VLU) [8]. The pathophysiology behind including deep vein thrombosis, perforator insufficiency, superficial and deep vein insufficiencies, arteriovenous fistulas, and calf muscle pump insufficiencies that lead to increased pressure in the distal veins of the leg and finally venous hypertension [9].



Fig. 1. (A) Signs of chronic venous insufficiency; (B) Chronic unhealed venous ulcer

CASE PRESENTATION

An 83-year-old unemployed male presented to Al-Sadder Teaching hospital, Misan, Iraq, with a chief complaint of right side leg painful swelling with the same side foot ulcer for the one-month duration. Leg swelling was gradually increasing that involved the whole limb with the involvement of the scrotum and causing limited movement of the right side lower limb. Foot ulcers also increased in size and became more irregular and fungating with the discharge of offensive smell whitish

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discharge. The patient was a heavy smoker. Past surgical history was right side leg swelling for the last six years and excision of the same ulcer one year ago but the histopathological report was lost and the family said that it was benign. Past medical history and family history were unremarkable. On examination, the patient presented with limping gate and pallor, his vital signs were normal, right side lower limb was unhealthy to inform of unhealthy thick skin, atrophy blanche, lipo-dermato-sclerosis, brown discoloration of the skin, unhealed ulcer, non-pitting edema, and eczema. Right side inguinal lymphadenopathy, scrotal swelling, right side leg power grade was four, and its distal pulses were intact.

The ulcer site is in the medial aspect of the ankle, just posterior and down to the medial malleolus. Size is 2 cm × 3 cm. Oval shape, with raised edges and everted with whitish discoloration. The base is firm, immobile, tender, red spots floor, and whitish offensive discharge. The surrounding tissues have induration of skin, and two scars of previously healed ulcers.

The complete blood picture and blood film morphology revealed hypochromic microcytic anemia of chronic disease, (Table 1). Color Doppler ultrasound of the right side lower limb venous system and right side inguinal area revealed multiple enlarged right side inguinal lymphadenopathy with loss of normal hilum and vascularity, markedly thickened

Tab. 1. Laboratory results of the blood investigation

Blood component	Results	Normal range
Hemoglobin	8.8 g/dl	11.0-16.0
HCT	30.6%	37.0-54.0
MCV	61.9 fl	80.0-100.0
WBC	$8.2 \times 10^9/L$	4.0-10.0
PLT	$344 \times 10^9/L$	150-450
ESR	51 mm/hr	2-18
RBS	121 mg/dl	90-160
Blood Urea	36 mg/dl	19-44

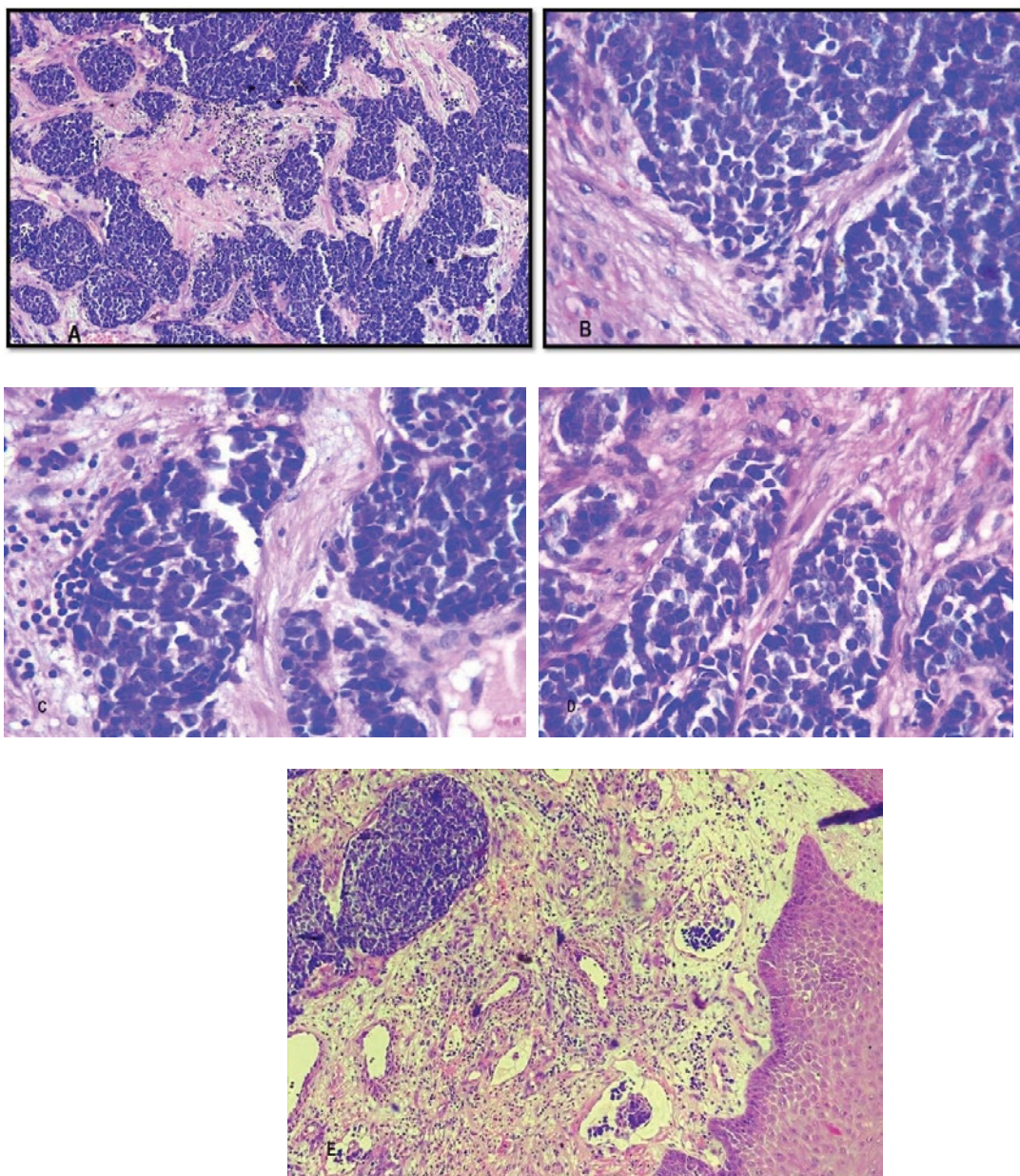


Fig. 2. (A) Haematoxylin and Eosin, X10, Merkel cell carcinoma; (B) Haematoxylin and Eosin (H and E), X40, mitosis (arrow); (C) Haematoxylin and Eosin (H and E), X40, nuclear crowding and molding; (D) Haematoxylin and Eosin (H and E), X40, cells have a scant eosinophilic cytoplasmic rim, vesicular nuclei with fine granular and dusty chromatin; (E) Haematoxylin and Eosin (H and E), X10, sparing of the epidermis with vascular invasion



Fig. 3. Progressive Deterioration After 30 days of tissue biopsy (A-C)

skin and subcutaneous tissues with edema, associated with compressed common femoral vein and superficial femoral vein otherwise deep venous thrombosis cannot be ascertained due to surrounding soft tissues swelling, patent popliteal vein with normal biphasic flow pattern, average diameter, good compressibility, limited augmentation likely due to external pressure. According to physical examination and color Doppler U/S, the patient has right side lower limb chronic venous insufficiency with CEAP classification [10] C6S, En, An, Pn (Figure 2A-2E).

Wound swab from the ulcer discharge was sent for culture and sensitivity which revealed the growth of *E. coli* that was highly sensitive to (Levofloxacin). Excisional biopsy from the unhealed ulcer and incisional biopsy from the right side inguinal lymph node were taken and sent for histopathological examination and immunohistochemistry study. The excisional biopsy revealed skin tissue with surface ulceration, necrotic debris, acute inflammation, and fibrous material. The underlying dermis infiltrated by nest sheets, and trabeculae of large fairly monotonous malignant cells with atypia and frequent mitosis, associated with intervening chronic inflammation (dominant lymphocytes). The differential diagnosis of this picture is Merkel-Cell Carcinoma (MCC), and poorly differentiated SCC. The incisional biopsy revealed fibrovascular tissue heavily infiltrated by chronic inflammation (lymphocytes), in between suspicious clusters of epithelial cells but with overlapped heavy basophilic nuclear material.

IHC examination for the tumor cells: the positive stains: Low molecular weight Keratin, CK20 (perinuclear dot-like staining), CD56, EMA, and neuron-specific enolase. The negative stains are High molecular weight cytokeratin, neurofilament, Chromogranin A, TTF1, and CD45/LCA.

From the history, examination, and IHC, the picture is consistent with Merkel Cell Carcinoma.

CT scan for neck, chest, abdomen and pelvis: Right side pelvic mass



Fig. 4. Tense right side leg at the date of MDT meeting just six days before the patient death

Staging

According to NCCN (National Comprehensive Cancer Network) guidelines version 2.2019, Clinical TNM classification of MCC for this patient is T2N1M1, Stage 4. T2 because the tumor size was 2 cm x 3 cm. N1 because there was metastasis to the regional inguinal lymph nodes. M1 because there was pelvic mass.

We reached the final diagnosis and staging after 50 days from the presentation. During that period the patient deteriorated progressively inform of progressive swelling of his right side leg, the appearance of multiple papules in that leg, loss of appetite, generalized weakness, dehydration, and renal impairment (Figure 3A-3C).

MDT team decided to start chemotherapy but because of the general condition, he was unfit, therefore; admitted to the hospital, for correction of anaemia and rehydration, but unfortunately, the patient died. The cause of death was a multi-organ failure despite supportive therapy.

DISCUSSION

This MCC case in the lower extremity of an elderly male patient with chronic edema has resulted in an extensive LN involvement with an aggressive pattern to death (Figure 4). The highly aggressive, MCC-specific mortality appears to be directly correlated to the microscopic spread, which follows the Halstedian model of spread with a stepwise spread to the regional LN before metastasizing hematogenously [11]. In our case, MCC was presented on the ground of a chronic venous insufficiency and with the gradually increasing lower extremity edema in the form of ulcerated, and enlarged lesions from the skin.

The venous stasis can cause newly appearing skin lesions suspicious for skin malignancies despite it is usually not possible to suspect MCC in a patient with chronic edema because chronic venous insufficiency and lymphedema are very rare etiological risk factors for MCC development [12]. The predominant anatomical sites that presented with MCC are areas with frequent sun exposure such as the skin of the face, upper limb, and shoulder, and lower limb and hip [13]. Microscopically, MCC is characterized by small and round to oval cells disposed of as either a dis-cohesive population or as cohesive clusters of cells. The tumor cells contain nuclei exhibiting finely granular and dispersed chromatin without prominent nucleoli, scant cytoplasm, in addition to intercellular junctions [14]. However, these cytomorphic characteristics are not specific to MCC as they could present in other malignancies such as melanoma, small cell carcinoma, and lymphoma [14]. In our case, the differential diagnosis of the histopathological features was MCC and poorly differentiated SCC, therefore; we send the biopsy again for IHC which allowed us for the identification of MCC.

The rarity of MCC and lack of comprehensive randomized

control studies hamper the establishment of guidelines for the therapy of those individuals.

In our case, MDT work suggested treatment with chemotherapy. Patient admitted to the hospital, but he died before chemotherapy after 6 days of final diagnosis and staging, these points showed highly aggressiveness of such case and poor prognosis.

CONCLUSION

Early diagnosis, especially in aggressive tumour, may increase the chance of treatment and can contributed to prognosis positively, therefore; the skin malignancies should be kept in mind in any newly developed skin lesion. The biopsy should be done for histopathological diagnosis when a clinically suspicious lesion is seen. Taking into account the frequency of cutaneous malignancies associated with Chronic Leg Ulcer (CLU).

DISCLOSURE STATEMENT

All authors declare no potential conflicts of interest related to the publication of this case report.

CONFLICT OF INTERESTS

The authors declare there is no conflict of interest.

ETHICAL APPROVAL

All procedures performed in this study were under the standards of the Helsinki Declaration and its later amendments.

PATIENT CONSENT

Written informed consent was obtained from all the included patients..

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