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Title: Merkel Cell Carcinoma on the Right Calf in Association with Chronic Lymphocytic Leukemia, Basal Cell Carcinoma, and Seborrheic Keratosis: a case report

Running title: Merkel Cell Carcinoma on the Right Calf

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Abstract

Merkel cell carcinoma (MCC) is a rare tumor with neuroendocrine origin. It presents as a single red nodule in the sun-exposed area by rapid and aggressive growth. This study presented a rare case of MCC on an unusual site, associated with chronic lymphocytic leukemia.

Keywords: Merkel Cell Carcinoma; Chronic Lymphocytic Leukemia, Neuroendocrine Tumors; Prognosis.

Introduction

Merkel cell carcinoma (MCC) is a rare tumor with aggressive neuroendocrine origin. Studies declared that MCC arises from merkel cells of basal layer of epidermis or hair follicles, stem cells of dermis, or precursor B cells [1]. About 0.13 to 1.6 per 100,000 persons are annually diagnosed with MCC, worldwide [2]. White elders, those who are under immunosuppressive treatments or have other malignancies, are more vulnerable to MCC. MCC mostly occurs as a painless red or purple nodule or solitary plaque, in the sun-exposed area (43% at head and neck, 24% at upper limbs and shoulders), with rapid and aggressive growth and poor prognosis [1, 3].

MCC is more common in men and in the seventies. It presents as local involvements (65%), regional lymph node metastasis (26%), and distant metastasis (8%) and has 30% mortality rate, worldwide. In this regard, diagnostic management of these patients requires the entire body examination of the lymph nodes, and all required laboratory tests or imaging in order to rule out differential diagnosis such as basal cell carcinoma (BCC), melanoma, epidermoid cysts. Consequently, it needs combined therapeutic managements [1, 4]. This study aimed to present a rare case of MCC, on an unusual site, associated with chronic lymphocytic leukemia (CLL) and its prognosis.

Case Presentation

Case history/ examination

A 69-year-old man reported to the dermatology clinic, with chief compliant of a single lesion on his inner region of right calf from six months ago. The lesion was firm, erythematous and non-eroded. It was enlarged three-fold during last month and caused discomfort. It was painless, non-pruritic, non-hemorrhagic, no secretion or smell. No color change was reported by the patient.

He had past medical history of BCC and Seborrheic keratosis on his face. There was no history of smoking, alcohol consumption, or family history of skin disease or malignancies. In systematic review, there was no evidence of significant weight lost. The vital signs were in the normal range and no fever was detected. In the physical examination, there was a nodule of 3.5×3.5×1.5 cm, sharp margin, stuck to the skin, exhibiting a pigmented papillomatosis surface. No signs or tenderness was observed on touch. (Figure 1) The conjunctiva was pale and no further remarkable sign was examined.

Differential diagnosis, investigations and treatment

In the following, a 2 × 3 mm section with 1 cm healthy margin was excised for pathological evaluation and labeled as excisional shine lesion biopsy. It showed that the skin section was accompanied with orthokeratotic epidermis. In addition, a lower layer of dermis with cell sheets, high nucleus-to-cytoplasm ratio, hyper chromatic nuclei and briefly pleomorphic with mitotic views, penetrating the collagen bundles of hypodermis and fat tissue were evident. A diagnosis of small round cell tumor was given. (Figure 2) Differential diagnoses of merkel cell carcinoma (MCC), B cell lymphoma (BCL), melanoma and also thyroid malignancy with skin manifestations, were made with the preference of MCC and recommended IHC staining. A panel

of IHC staining demonstrated positive stains for Chromogranin, Neuron-specific enolase (NSE), cytokeratin (CK20) and Synaptophysin. It also reported negative stains for transcription termination factor 1 (TTF-1) (rule out thyroid malignancies), S100 protein (rule out melanoma), and B-lymphocyte antigen (CD 20) protein (rule out BCL).

The ultrasound of both groins was revealed the presence of multiple lymph nodes with thick and hyper vascular cortex, and central and peripheral vascular flow in the right inguinal (the largest lymph node was 27×19×31 mm), which strongly suggestive of malignancy. In this regard, 45 lymph nodes at right inguinal with 20×10×5 cm area was removed by a plastic surgeon.

A spiral computed tomography (CT) scan of the abdomen with intravenous (IV) and oral contrast showed no findings in favor of pulmonary involvement. A maximum transverse diameter of 34 mm was reported around the inferior vena cava (IVC), causing the IVC to move anteriorly and narrow the stenosis. No clear lytic or bony blast lesion was reported.

Laboratory tests demonstrated WBC=61.500 (Neutrophil=7.4, lymphocyte=85.5), Hb=9.7, Hct=31.9, MCV=85, MCH=25.7, MCHC=30.3, RDW=14.4, ALKP=323 and LDH = 1981. The peripheral blood smear test showed the smudge cell, suggestive of lymphoproliferative disorders in accordance with CLL, and recommended immunophenotyping. Therefore, Flow cytometry reported lymphoproliferative B cell disorder with 88% B cell and 3% T cell. Immunophenotyping noted markers of CD 5+, CD 19+, CD 20 +, and CD 23 +, which was suggestive of CLL of B cell type.

Outcome and follow-up

The patient was scheduled for chemotherapy medications including IV Etoposide (120 mg/day) and IV Cisplatin (150 mg/day) for 3 days repeated every 3 weeks. Three months later, a thoracic

contrast-enhanced CT scan showed multiple adenopathy with large calcification (transverse diameter of 15 mm in the mediastinum) and ninety prominent lymph nodes on the axillary ligaments of both sides. Scattered sclerotic lesions were observed in dorsal part of metastatic lumbar vertebrae, right iliac wing, middle sacrum, right femoral head, and inferior ramus of left pubis. Despite all diagnostic and treatment procedures performed for this patient, he died after nine months which may be due to the old age, gender, rapid growth and metastasis of MCC, and its association with several cancers and skin disease.

Discussion

MCC is a rare skin neoplasm and mostly missed diagnosis, due to its various histopathologic differential diagnoses. In addition, it has aggressive behavior and rapid growth thus leads to multidisciplinary approaches. IHC and lymph node evaluation play important roles for MCC management. MCC is composed of round tumor cell with high nuclei to cytoplasm ratio. It mostly stains positive for CK epithelial membrane antigen and neuroendocrine markers such as NSE, chromogranin, synaptophysin and CD56. Among these, CK20 is more specific for MCC [1]. The recommended treatment for MCC is wide local excision with a healthy margin of 1 to 3 cm with adjacent therapies. Studies showed that MCC has local recurrence, local lymph node metastasis, and distant metastasis rates of 20% to 75%, 31% to 80% and 26% to 75%, respectively [5, 6]. Others stated that the recurrence rate of MCC after the lesion excision was 22% to 200% [7, 8]. Risk factors for bad prognosis were as follows: old of age, males, primary size of MCC more than 2 cm, location in the lower extremities, lymph node involvement and late referral of patient (more than three months) [9, 10].

In this study, a known case of BCC and Seborrheic keratosis on the face was diagnosed with MCC in non-sun exposed site, accompanied with CLL.

The association of MCC with other malignancies is still a matter of debate. A study among 1306 patients with MCC and 2048739 patients with other primary cancers showed that those with primary MCC were at 1.22 times higher risk of developing a subsequent cancers (at salivatory, liver or gallbladder), especially at first year of diagnosis but CLL was not significantly associated with primary MCC. On the other hand, those with other malignancies (especially with CLL) were at 1.36 times higher risk of developing secondary MCC [11, 12]. In this regard, a study reported a non-immunosuppress host of CLL with secondary MCC [13]. On the other hand, a study

assessed the association between CLL and other malignancy among 4164 patients with CLL and declared that although CLL was significantly associated with various other malignancies, concomitant of MCC was only observed in six patients [14]. This brings up the importance of contaminant malignancies associated with primary or secondary MCC in order to enhance the prognosis.

Conclusion

This study presented a rare case of MCC in a patient with several malignancies and skin disease and its poor prognosis in order to enhance the physicians' knowledge about MCC and its companions. Therefore, the rare and atypical manifestations of MCC should be always considered by physicians, especially in a patient with several risk factors, and conflict with other malignancies. **Author contributions**

All authors contributed to the study conception and design. Material preparation, data collection and acquisition were performed by Sepideh Karkon-Shayan, Abolfazl Zare, and Hamideh Mohammadzadeh. The first draft of the manuscript was written by Sepideh Babaniamansour, Mohammadreza Majidi and, Mohammad Dehghani Firouzabadi, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethic Approval

This study was approved by the Ethic Committee of Gonabad University of Medical Sciences, Gonabad, Iran. Additionally, informed consent was obtained from the patient.

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Conflicts of Interest Statement

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Figure legends

1- Pigmented papillomatosis nodule on inner region of right calf (before and after surgery)

2- Microscopic examination revealed small round cell tumor. Orthokeratotic epidermis, lower layer of dermis with cell sheets, high nucleus-to-cytoplasm ratio, hyper chromatic nuclei and briefly pleomorphic with mitotic views (HE × 20).