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**Ectopic Cushing syndrome in a patient with metastatic Merkel Cell Carcinoma: A case report**

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**Abstract**

**BACKGROUND**

Background

Ectopic Cushing syndrome (ECS) is a rare condition commonly associated with neuroendocrine tumors (NET), mainly bronchial carcinoids. The association of paraneoplastic syndrome with Merkle Cell Carcinoma (MCC) is limited to individual case reports.

**CASE SUMMARY**

In this article we report an unusual and striking presentation of ECS in a patient with known metastatic MCC. An elderly patient presented with new onset severe hypertension, hyperglycemia and hypokalemia, muscle wasting and peripheral edema. The diagnosis of ACTH dependent, non-pituitary, Cushing syndrome was established. Medical therapy inhibiting adrenal function was promptly started but unfortunately the patient survived only a few days after diagnosis.

**CONCLUSION**

Conclusion

The occurrence of an aggressive form of ECS in patients with NET should be recognized as an ominous event. To our knowledge, the association of this complication in a patient with MCC had not been reported.

## **INTRODUCTION**

Merkel cell carcinoma (MCC) is an uncommon but highly aggressive skin cancer with neuroendocrine features (1). It was first described by Toker in 1972 as "trabecular carcinoma of the skin" (2). Evidence suggests that its incidence and mortality are increasing across the world (3). Ectopic Cushing syndrome (ECS) is a rare condition due to ectopic production of ACTH by non-pituitary tumors. The ACTH-producing neoplasms usually originate from neuroendocrine tumors (NET) and can present as benign indolent tumors or aggressive metastatic tumors with poor prognosis (4). Although in the past elevated ACTH levels in plasma and tumoral tissue were demonstrated in patients with MCC (5,6), there are no report of ACTH-producing MCC that fulfill the diagnostic criteria for ECS. We describe a patient with metastatic MCC who developed an aggressive form of ECS.

## **CASE PRESENTATION**

### ***Chief complaints***

A 82-year-old man with a 2-year history of MCC was referred for evaluation and treatment of uncontrolled high blood pressure and new onset hyperglycemia.

### ***History of present illness***

In 2018 a cervical lymphadenopathy biopsy showed metastatic MCC with no apparent primary cutaneous lesion (Figure 1). Multiple bone metastases were demonstrated by <sup>18</sup>F (18-fluorodeoxyglucose) PET/CT scan (<sup>18</sup>FDG-PET/CT). No pathological uptake was seen in lungs. The patient achieved good response on avelumab initially as disclosed by significant reduction of uptake intensity in cervical lymph node and in the skeleton on subsequent <sup>18</sup>FDG-PET/CT scan. But thereafter, the disease progressed

despite adjuvant radiotherapy and systemic therapy including etoposide, carboplatin and topotecan. Indeed, <sup>18</sup>FDG-PET/CT scan showed intensification of the uptake in bones, and new metastases in mediastinal lymph nodes and multiple cutaneous lesions. Noticeably, no disease was present in lungs.

### *History of past illness*

His history was significant for multiple surgical <sup>1</sup> treatments for squamous cell carcinoma and basal cell carcinoma of the skin.

### *Personal and family history*

multiple surgical <sup>1</sup> treatments for squamous cell carcinoma and basal cell carcinoma of the skin.

### *Physical examination*

Physical examination revealed a high blood pressure (198/100), and a 4 cm-sized purplish-blue tumor in his central chest (Figure 2), bilateral axillary lymphadenopathy, and bilateral lower extremities pitting edema. The clinical phenotype was dominated by weight loss and muscle wasting.

### *Laboratory examinations*

Initial blood work revealed a glucose level of 241mg/dL with hypokalemia (2.7nmol/L (

The 24-hour free urine Cortisol level was 9986 nmol/24hr (normal values: 57.7-806.8). After high dose (8 mg) overnight dexamethasone suppression test (HDST), the 8-am serum cortisol was 44.9 μg/dL (normal values: 4.3-22.4). Serum ACTH level was elevated :106 pg/mL (0.0-46).

Testing with intravenous Corticotropin releasing hormone (CRH) administration did not affect ACTH or cortisol levels, which is typical of ECS (Table 1)

### *Imaging examinations*

Magnetic resonance imaging (MRI) scan of the pituitary gland was normal.

### **FINAL DIAGNOSIS**

Ectopic ACTH dependent Cushing's syndrome

### **TREATMENT**

The patient was treated with ketoconazole

### **OUTCOME AND FOLLOW-UP**

His blood pressure and glucose levels were normalized, however, his general state did not allow additional antineoplastic therapy and he died within few days.

### **DISCUSSION**

We present a 82-year patient with a metastatic MCC presenting with an overwhelming form of ECS. ECS is a rare condition which accounts for about 10-20% cases of ACTH-dependent Cushing syndrome. Neuroendocrine tumors (NETs), principally bronchial carcinoids, are the most frequent causes of ECS. Less frequent causes are thymic carcinoids and pancreatic (p) NETs (7). Small cell lung carcinoma is a known cause of ECS, but in our patient imaging studies did not reveal any lung lesions. Recently a case of metastatic NET of unknown origin presenting with ECS was reported (8). Several manifestations of MCC-associated paraneoplastic syndromes have been reported (9), but ECS associated with MCC has not be described, even though a case of metastatic MCC within a cortisol-producing adrenal adenoma has been recently reported (10). The time elapsed between the first symptoms of hypercortisolism and the diagnosis of ECS may predict the prognosis of the underlying malignancy. The shorter it is, the poorer is the prognosis. In addition to the grade of NET, the severity of cortisol excess is an independent negative prognostic factor (7). The molecular mechanisms underlying

ECS-associated malignant tumors include aberrant processing of proopiomelanocortin (POMC) gene leading to release in the circulation of high molecular weight ACTH precursors like POMC and pro-ACTH. It is speculated that the ability of the tumor to express aberrant molecules is related to the progression of the disease (11). If ectopic ACTH-producing malignancy is diagnosed early as a localized disease, surgical removal of the primary tumor is the treatment of choice, but it is rarely achievable in patients with aggressive neoplasms. In this ECS group a prompt control of hypercortisolism should be attempted by medical treatment or alternatively by adrenalectomy (4).

### **CONCLUSION**

MCC and neuroendocrine ECS are both rare conditions. The occurrence of ECS in patients with metastatic NETs is a major cause of poor prognosis. The suspicion of Cushing syndrome should receive adequate attention and prompt evaluation to confirm the diagnosis and initiate rapidly the treatment to attain a more favorable prognosis.

## ORIGINALITY REPORT

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