Case Report

Ectopic ACTH Production Caused by Metastatic Parotid Gland Acinic Cell Carcinoma

Jacob M. Burch, DO *, James S. Choi, DO, Osama Mosalem, MD, Lawrenshey Charles, DO

Sparrow Hospital, Michigan State Internal Medicine Residency, Swartz Creek, Michigan

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A B S T R A C T

Objective: To present a case of adrenocorticotropic hormone (ACTH) hypersecretion caused by a metastatic acinic cell carcinoma (AcCC) of the parotid. Only 6 cases have been reported prior to October 2019. We believe that this condition is under-reported and hope that improved recognition will improve its reporting.

Methods: Diagnosis in this case was done using surgical pathology of the primary tumor, involving lymph nodes, and a metastatic lesion. Following an initial misdiagnosis, a final diagnosis of AcCC was made using immunohistochemical staining. ACTH hypersecretion was diagnosed by testing for random ACTH, cortisol, and 24-hour urine aldosterone and cortisol levels.

Results: A 57-year-old man presented with hypokalemia, lower-extremity edema, and left-side rib pain 7 months following excision of a 4-cm left-parotid tumor. Immunostaining positive for DOG-1, CK7, pan-cytokeratin (including CAM5.2), and SOX10 led to the diagnosis of AcCC. ACTH hypersecretion was diagnosed based on a random ACTH level of 307 pg/mL (normal morning value, 7.2-63 pg/mL), a cortisol level of 33 mg/dL (normal morning value, 4.3-19.8 mg/dL; normal PM value, 3.1-15.0 mg/dL), a 24-hour urine aldosterone level of <0.7 U (normal, 2.0-20 U), and a 24-hour urine cortisol level of 4564 U (normal, 3.5-45 U). The patient’s ACTH hypersecretion and hypokalemia were treated with potassium replacement, amiloride, and ketoconazole. His metastatic recurrence was treated with radiotherapy, chemotherapy, and immunotherapy. The patient died after being diagnosed with sepsis secondary to multifocal postobstructive pneumonia 4 months after the diagnosis of his metastatic recurrence.

Conclusion: Ectopic ACTH production caused by metastatic AcCC is a rare phenomenon but has been increasingly described over the last 15 years. We believe that this condition likely has a greater prevalence than what is reported and that improved recognition will lead to improved outcomes.

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Introduction

Acinic cell carcinoma (AcCC) is an uncommon form of salivary gland tumor most commonly occurring in the parotid gland. Although rare, metastatic AcCC has been observed to lead to ectopic ACTH production. There have previously been 6 cases of this described condition. We report the seventh case of metastatic AcCC leading to ectopic ACTH production and review the characteristics of each of the published cases.

Case Report

A 57-year-old man presented with a left-parotid mass that had been enlarging over a period of 3 months. He underwent fine-needle aspiration (FNA), which yielded negative results for malignancy. Following the negative FNA result, computed tomography (CT) of the neck with a contrast agent showed an irregular, heterogeneously enhancing, 2.8-cm left-parotid mass with 2 abnormal-appearing level-2 lymph nodes without enlargement. Following the CT, the patient underwent left superficial parotidectomy. During the procedure, frozen-section pathology suggested a high-grade mucoepidermoid carcinoma, and a decision was made to proceed with total parotidectomy with a modified left-side neck dissection. Final surgical pathology resulted in the diagnosis of high-grade mucoepidermoid carcinoma measuring 4 cm and with focally positive margins and 3 of 16 lymph nodes positive for the metastatic disease (stage IVA, T2, N2b, M0).
Following the surgical resection, a positron emission tomography (PET) scan was performed, which showed no evidence of metabolically active metastatic disease. The patient underwent adjuvant radiation therapy for the left-parotid tumor bed and draining lymph nodes, which was completed 2 months following the surgical therapy.

Two months following the completion of the radiation therapy, the patient complained of focal left-side rib pain with significant tenderness during a follow-up with his oncologist. Chest CT with an intravenous contrast agent showed no evidence of metastatic disease. The patient returned 5 months later and complained of continued left-lateral-rib pain and bilateral lower-extremity edema. The patient had been seen by his cardiologist in the interim for the edema and had been started on furosemide, with some improvement. Despite potassium replacement, the patient developed hypokalemia, and his furosemide and potassium were discontinued. Spironolactone and chlorthalidone were added. Given his continued rib pain and edema, a comprehensive metabolic panel (CMP) and PET-CT were performed as part of the evaluation for the metastatic disease. CMP showed a potassium concentration of 3.2 mEq/L (normal, 3.5–4.9 mEq/L) and an alanine aminotransferase level of 55 U/L (normal, 3–45 U/L). The PET-CT showed 18F-fluorodeoxyglucose-avid metastatic pulmonary nodules, lymphadenopathy, and sclerotic lesions of the left seventh-rib, thoracic spine, left ilium, and sacrum. Following the results of the PET-CT, a plan was made to obtain a biopsy of the left seventh-rib lesion. CMP performed 2 days later showed worsening hypokalemia with a potassium concentration of 2.2 mEq/L, resulting in the patient getting hospitalized for aggressive potassium replacement. Despite initially receiving 160 mEq of combined oral and intravenous potassium, the patient’s potassium concentration dropped further to 1.9 mEq/L. After an additional 320 mEq of potassium, CMP showed a potassium concentration of 3.3 mEq/L. A random ACTH level was measured at 12:00 PM and was 307 pg/mL (normal morning value, 3.7–63 pg/mL). A cortisol level measured at the same time was 33 µg/dL (normal morning value, 4.3–19.8 µg/dL), normal PM value, 3.1–15.0 µg/dL). His 24-hour urine aldosterone level was below the lower cutoff limit of the laboratory value of <0.7 µg/dL (normal, 2.0–20), and the 24-hour urine cortisol level was 4564 µg/dL (normal, 3.5–45). CT-guided biopsy of the patient’s left seventh-rib sclerotic lesion was performed while he was hospitalized. Following stabilization of the patient’s hypokalemia and correction of his hypertension with a regimen of potassium at 200 mg daily, losartan at 100 mg daily, and spironolactone at 100 mg daily, the patient was able to be discharged.

Pathologic evaluation of the left seventh-rib lesion found a metastatic carcinoma consistent with a known high-grade mucoepidermoid carcinoma of the parotid. The patient’s oncologist consulted an oncology specialist from another institution, and an intravascular contrast agent showed no evidence of metastatic disease. The patient returned 5 months later and complained of continued left-lateral-rib pain and bilateral lower-extremity edema. The patient had been seen by his cardiologist in the interim for the edema and had been started on furosemide, with some improvement. Despite potassium replacement, the patient developed hypokalemia, and his furosemide and potassium were discontinued. Spironolactone and chlorthalidone were added. Given his continued rib pain and edema, a comprehensive metabolic panel (CMP) and PET-CT were performed as part of the evaluation for the metastatic disease. CMP showed a potassium concentration of 3.2 mEq/L (normal, 3.5–4.9 mEq/L) and an alanine aminotransferase level of 55 U/L (normal, 3–45 U/L). The PET-CT showed 18F-fluorodeoxyglucose-avid metastatic pulmonary nodules, lymphadenopathy, and sclerotic lesions of the left seventh-rib, thoracic spine, left ilium, and sacrum. Following the results of the PET-CT, a plan was made to obtain a biopsy of the left seventh-rib lesion. CMP performed 2 days later showed worsening hypokalemia with a potassium concentration of 2.2 mEq/L, resulting in the patient getting hospitalized for aggressive potassium replacement. Despite initially receiving 160 mEq of combined oral and intravenous potassium, the patient’s potassium concentration dropped further to 1.9 mEq/L. After an additional 320 mEq of potassium, CMP showed a potassium concentration of 3.3 mEq/L. A random ACTH level was measured at 12:00 PM and was 307 pg/mL (normal morning value, 3.7–63 pg/mL). A cortisol level measured at the same time was 33 µg/dL (normal morning value, 4.3–19.8 µg/dL), normal PM value, 3.1–15.0 µg/dL). His 24-hour urine aldosterone level was below the lower cutoff limit of the laboratory value of <0.7 µg/dL (normal, 2.0–20), and the 24-hour urine cortisol level was 4564 µg/dL (normal, 3.5–45). CT-guided biopsy of the patient’s left seventh-rib sclerotic lesion was performed while he was hospitalized. Following stabilization of the patient’s hypokalemia and correction of his hypertension with a regimen of potassium at 200 mg daily, losartan at 100 mg daily, and spironolactone at 100 mg daily, the patient was able to be discharged.

Pathologic evaluation of the left seventh-rib lesion found a metastatic carcinoma consistent with a known high-grade mucoepidermoid carcinoma of the parotid. The patient’s oncologist consulted an oncology specialist from another institution, and a histopathologic review of the patient’s primary parotid tumor and the left seventh-rib bone biopsy, it was perceived that the patient’s disease most likely represented high-grade AcCC, as opposed to the previously diagnosed mucoepidermoid carcinoma. The pathology samples of the parotid gland, lymph nodes, and seventh-rib lesion were then sent to a third institution, which agreed with the corrected diagnosis of dedifferentiated AcCC. This diagnosis was based on the parotid tumor’s immunohistochemical staining positive for DOG-1, CK7, pan-cytokeratin (including CAM5.2), and SOX10. P63 immunostaining was weak, with patchy staining showing uncertain clinical significance. The left seventh-rib biopsy immunostaining was positive for DOG-1 and pan-cytokeratin (including CAM5.2) and negative for p63. Staining for ACTH was not completed at that time.

The patient was started on palliative chemotherapy with a combination of carboplatin, fluorouracil, and cetuximab in addition to palliative radiotherapy for his left seventh-rib metastatic lesion. Following progression of the metastatic lesions despite 2 cycles of carboplatin, fluorouracil, and cetuximab, the patient was started on immunotherapy with pembrolizumab. Zoledronic acid was started in addition to the patient’s previous calcium and vitamin D supplementation because of his bone metastasis. The patient was also started on amiloride at 5 mg daily, and with this addition, he was able to be tapered to 120 mEq of potassium daily. The patient’s hypokalemia subsequently worsened, requiring stepwise titration of the potassium replacement to 360 mEq daily. Ketoconazole at 200 mg twice daily was prescribed on an outpatient basis for his persistently elevated ACTH and cortisol levels (Table 1) along with a continued difficulty in managing the patient’s hypertension and hypokalemia.

Approximately 4 months following the diagnosis of the metastatic recurrence (9 days after starting ketonozole), the patient was hospitalized for episodic generalized weakness. His symptoms were thought to be due to recurrent electrolyte derangements, which improved, to a degree, with aggressive replacement. No changes were made in his ketonozole, amiloride, losartan, or spironolactone doses. The patient was discharged to an inpatient rehabilitation facility. The following day, the patient developed acute hypoglycemia, tachycardia, and acute hypotension. Zoledronic acid was started to the hospital, where he was diagnosed with sepsis secondary to multifocal postobstructive pneumonia. CT of the chest revealed multifocal metastatic disease of the lungs in addition to the consolidations. The patient was started on broad-spectrum antibiotics, but he continued to deteriorate. A decision to end the aggressive care and pursue only comfort measures was made by the patient and his family. The patient died 3 days later.

**Discussion**

In this case, the 57-year-old man presented with hypertension, hypoglycemia, and rib pain 4 months after having undergone surgical excision of a parotid tumor, which was followed by radiation therapy. The patient was found to have severe elevations of ACTH and cortisol levels that were the cause of his hypertension and hypokalemia. His rib pain was found to be due to metastatic disease. Upon review of his initial tumor and metastatic lesion, his diagnosis was changed from mucoepidermoid carcinoma to dedifferentiated AcCC of the parotid. Despite treatment, which included chemotherapy, radiation therapy, and immunotherapy directed toward his metastatic cancer, as well as supportive care and ketoconazole directed toward his ectopic ACTH production and subsequent Cushing syndrome, the patient continued to deteriorate until he died 2 months following the diagnosis of his metastasis.

AcCC is defined by the World Health Organization as “a malignant epithelial neoplasm of salivary glands in which at least some of the neoplastic cells demonstrate serous acinar cell differentiation, which is characterized by cytoplasmic zymogen secretory granules. Salivary ductal cells are also a component of this neoplasm.” AcCC represents 1% to 7% of salivary gland tumors and 7% to 15% of salivary gland malignancies. Over 90% of AcCCs occur in the parotid gland. A 2013 review of the United States National Cancer Institute’s Surveillance, Epidemiology, and End Results registry found AcCC to have a female predominance, with a 1:47:1 female-to-male ratio. The Surveillance, Epidemiology, and End Results registry data also demonstrated that 68% of patients with AcCC are >40 years of age, with 33% of cases occurring between the ages of 40 to 59 years, and that 35% of the cases occur in patients >60 years of age. The most common presentation of AcCC is a slow-growing, painless parotid mass. The diagnosis is complicated, often with benign-appearing imaging, and has low
sensitivity and specificity of FNA, as seen in this case. Given the poor diagnostic strength of other modalities, the diagnosis of AcCC should be based on surgical pathology. The cornerstone of the treatment of AcCC is surgical resection, where the extent of the resection and choice of whether or not to resect the facial nerve are dictated by the degree of tumor invasion. Adjuvant radiotherapy should be restricted for use in high-risk patients because it does not improve survival when used in 1 case. Supportive care directed toward hypertension, hyperkalemia, and/or hyperglycemia was employed in all 6 cases.

Although rare, AcCC has been associated with ectopic ACTH production. This phenomenon was first described in 1970, and 5 additional cases were reported between 2007 and October 2019. This increase in the reported cases likely represents improved recognition of the capability of AcCC to stimulate ACTH production. In each of these cases, the patient had a metastatic recurrence of their initial disease. The most common chief complaints in these patients were peripheral edema (5 of 7) and hypertension (3 of 7), followed by confusion, hypokalemia, fatigue, and weakness (2 of 7). Upon initial hospital evaluation, 6 of these 7 patients were found to be hypertensive, with no mention of blood pressure in the remaining case. In all 7 cases, the patients were found to be hypokalemic. The potassium values ranged from 1.8 (no units reported) to 3.1 mEq/L. The ACTH value in each of these patients was markedly elevated, with values ranging from 1.7 to 15.6 times the upper limit of the normal value in the 5 cases with normal ranges. Likewise, marked elevations in the cortisol level were also reported, using several different methods. Of the 6 cases in which the cortisol level was measured, values ranging from 2.9 to 94.7 times the upper limit of the normal value were reported.

### Table 1

| Year Published | Age | Initial Therapy | Time from initial diagnosis to ectopic ACTH diagnosed (mo) | Location of Metastasis | Outcome |
|---------------|-----|----------------|----------------------------------------------------------|------------------------|---------|
| Cox et al11    | 1970 | 44 M | Total parotidectomy, radical neck dissection | 13 | Pulmonary vessels, liver, pancreas | Died |
| Jaimesson et al5,6 | 2007 | 62 F | Total parotidectomy, neck dissection, adjuvant radiotherapy | 8 | "Widely metastatic" | Died |
| Butt et al12 | 2008 | 60 M | Parotidectomy, neck dissection, adjuvant radiotherapy | 2 | Mediastinal and hilar lymph nodes | Alive at the time of publication | Died |
| Shenoy et al5 | 2011 | 52 F | Total parotidectomy, neck dissection, adjuvant radiotherapy | 6 | "Widespread visceral metastasis" | Died |
| Dacruz et al13 | 2016 | 60 F | Surgical excision | 36 | Ischium | Died |
| Saluja et al2 | 2019 | 58 M | Total parotidectomy, modified neck dissection, hemithyroidectomy, adjuvant radiotherapy | 6 | Supraclavicular, subcarinal, precardial, mediastinal, hilar lymph nodes, lung, bone | Lost to follow-up |
| Present caseb | 2020 | 57 M | Total parotidectomy, modified neck dissection, adjuvant radiation | 7 | Lung, mediastinal lymph nodes, left 7th rib, thoracic spine, left ilium, sacrum | Died |

Abbreviation: ACTH = adrenocorticotropic hormone.

### Table 2

| Case | Blood pressure | Potassium | ACTH | Serum cortisol | Urinary cortisol |
|------|---------------|-----------|------|---------------|-----------------|
| Cox et al11 | 150/80 | 2.2 mEq/L | 547 pg/mL (<120) | 118 (8-12) | 10 700 µg/d (20-90) |
| Jamieson et al5,6 | "mild hypertension" | 1.8 (no units) | 153 (no units or normal) | 1358 | ... |
| Butt et al12 | NR | 2.4 mmol/L | 106 ng/L (<40) | 1575 nmol/L (171-536) | 15 374 nmol/d (<280) |
| Shenoy et al5 | 180/105 | 2.5 mmol/L | 810 nmol/L (10-50) | 4734 nmol/L (<50) | 21 300 nmol/d (<150) |
| Dacruz et al13 | "elevated" | 2.6 mmol/L | 106 ng/L (7-63) | ... | 4481 nmol/d (<146) |
| Saluja et al2 | 187/112 | 3.1 mEq/L | 263 pg/mL (0-46) | 95.2 µg/dl (6.2-19.4) | ... |
| Present caseb | 156/99 | 2.2 mEq/L | 307 pg/mL | 33 µg/dl | 4564 µg/d (3.5-45) |

Abbreviation: ACTH = adrenocorticotropic hormone.

Normal values ranges are in parenthesis

Normal range not reported.

Serum ACTH and cortisol samples obtained outside of times listed for normal lab values.

### Table 3

| Study | Year Published | Age | Sex | Initial Therapy | Time from initial diagnosis to ectopic ACTH diagnosed (mo) | Location of metastasis | Outcome |
|-------|----------------|-----|-----|----------------|----------------------------------------------------------|------------------------|---------|
| Cox et al11 | 1970 | 44 M | Total parotidectomy, radical neck dissection | 13 | Pulmonary vessels, liver, pancreas | Died |
| Jamieson et al5,6 | 2007 | 62 F | Total parotidectomy, neck dissection, adjuvant radiotherapy | 8 | "Widely metastatic" | Died |
| Butt et al12 | 2008 | 60 M | Parotidectomy, neck dissection, adjuvant radiotherapy | 2 | Mediastinal and hilar lymph nodes | Alive at the time of publication | Died |
| Shenoy et al5 | 2011 | 52 F | Total parotidectomy, neck dissection, adjuvant radiotherapy | 6 | "Widespread visceral metastasis" | Died |
| Dacruz et al13 | 2016 | 60 F | Surgical excision | 36 | Ischium | Died |
| Saluja et al2 | 2019 | 58 M | Total parotidectomy, modified neck dissection, hemithyroidectomy, adjuvant radiotherapy | 6 | Supraclavicular, subcarinal, precardial, mediastinal, hilar lymph nodes, lung, bone | Lost to follow-up |
| Present caseb | 2020 | 57 M | Total parotidectomy, modified neck dissection, adjuvant radiation | 7 | Lung, mediastinal lymph nodes, left 7th rib, thoracic spine, left ilium, sacrum | Died |

Abbreviation: ACTH = adrenocorticotropic hormone.
Adrenalectomy has not yet been employed as a therapeutic option for Cushing syndrome secondary to ectopic ACTH production in the setting of AcCC.\textsuperscript{2,5,11-13}

Five of the 7 reported patients with ectopic ACTH production from AcCC were deceased at the time when their case was reported. One case was lost to follow-up.\textsuperscript{2} The remaining case reports did not describe the duration of follow-up for the patients after they were found to have ectopic ACTH production, making it unclear whether the outcome did indeed differ from that of the other described cases.\textsuperscript{13} Of the patients who died, 3 died following infections leading to sepsis, 1 died following uncontrolled bleeding leading to a cardiac arrest after the resection of a posterior neck mass, and the cause of death of the remaining case was not stated.\textsuperscript{2,5,11,13}

**Conclusion**

Ectopic ACTH production caused by AcCC most often presents with vague symptoms requiring a high degree of suspicion to make a timely diagnosis. These characteristics include peripheral edema, hypertension, confusion, fatigue, weakness, and hypokalemia. We hope that improved recognition of this condition, especially by oncologists and primary care physicians who see these patients most commonly, will lead to earlier diagnosis and treatment of ACTH hypersecretion and the metastatic disease that underlies it.

**Disclosure**

The authors have no multiplicity of interest to disclose.