doi:10.2478/enr-2025-0031

# Hypokalemic metabolic alkalosis as a clinical clue to ectopic ACTH syndrome: two cases of neuroendocrine carcinoma

Cundullah Torun, Erhan Eken, Bahar Cakir, Mehmet Uzunlulu

*Department of Internal Medicine, Goztepe Training and Research Hospital, Istanbul Medeniyet University, Kadikoy/Istanbul, Turkey*
*E-mail: cundullaht@gmail.com*

**Objective.** Ectopic adrenocorticotropic hormone (ACTH) syndrome (EAS) is a rare, but potentially life-threatening cause of Cushing's syndrome. Its clinical recognition may be delayed, especially when classical features of hypercortisolism are absent. We present two cases, in which hypokalemic metabolic alkalosis was the initial and main clinical clue leading to the diagnosis of neuroendocrine carcinoma with ectopic ACTH production.

**Case 1.** The first case was a 71-year-old woman admitted with progressive weakness, gait disturbance, and uncontrolled hypertension. Laboratory tests revealed severe hypokalemia and metabolic alkalosis. Endocrine evaluation showed markedly elevated urinary free cortisol and plasma ACTH, with absent suppression on low-dose dexamethasone testing. Colonoscopy for anemia revealed a rectal mass and histopathology confirmed poorly differentiated neuroendocrine carcinoma. Imaging demonstrated widespread metastases. Despite supportive treatment, she died of multi-organ failure during hospitalization.

**Case 2.** The second case was a 67-year-old woman presenting with fatigue, weakness, and weight loss. Laboratory findings included hypokalemia, metabolic alkalosis, renal dysfunction, and elevated liver enzymes. Hormonal studies again confirmed ACTH-dependent Cushing's syndrome without suppression on dexamethasone testing. Imaging revealed a right hilar lung mass and bronchoscopy with biopsy confirmed small-cell neuroendocrine carcinoma. PET-CT showed disseminated metastases. Although chemotherapy was initiated, she developed rapid progression and died shortly thereafter.

**Conclusion.** These cases highlight that severe hypokalemic metabolic alkalosis may represent the primary manifestation of ectopic ACTH syndrome even in the absence of overt Cushingoid features. Recognition of this biochemical pattern should prompt consideration of neuroendocrine tumors allowing earlier diagnosis and timely therapeutic intervention in this aggressive condition.

**Keywords:** hypokalemia, metabolic alkalosis, ectopic ACTH, Cushing's syndrome, neuroendocrine carcinoma

Cushing's syndrome is a rare endocrine disorder resulting from chronic cortisol excess. It is etiologically classified as adrenocorticotropic hormone (ACTH) dependent, which occurs due to ACTH-secreting pituitary adenoma or less commonly, non-pituitary ectopic ACTH-secreting tumors, and as ACTH-independent, which develops in the presence of benign or malignant adrenal tumors or bilateral adrenal hyperplasia (Gadelha et al 2023). Tumors secreting ACTH outside the pituitary gland account for 10–20% of ACTH-dependent cases. The most frequent primary sites are the lungs, with pulmonary

**Corresponding author:** Cundullah Torun MD, Department of Internal Medicine, Goztepe Training and Research Hospital, Istanbul Medeniyet University, Kadikoy/Istanbul, Turkey; fax: +90 216 606 52 10; phone: +905497949993; e-mail: cundullaht@gmail.com.

neuroendocrine tumors responsible for approximately 25% of cases and small-cell lung carcinoma for about 20%. Other causes include thymic and pancreatic neuroendocrine tumors, medullary thyroid carcinoma, pheochromocytoma, and paraganglioma (Kamp et al. 2016).

Neuroendocrine tumors (NETs) are neoplasms derived from neuroendocrine cells that can produce bioactive substances. They display heterogeneity in biological behavior, histological features, and treatment response. They are often asymptomatic and incidentally detected at diagnosis. The reported incidence of NETs has been rising in recent decades and these tumors are associated with considerable morbidity and mortality. Epidemiological studies have indicated that age, sex, tumor morphology, stage, site, and low socioeconomic status are independent predictors of survival (Dasari et al. 2017; White et al. 2022).

Metabolic alkalosis is a common acid-base disorder among hospitalized patients. It is defined by an elevation in serum bicarbonate and arterial pH accompanied by a compensatory rise in $PCO_2$ due to adaptive hypoventilation. Severe metabolic alkalosis (arterial pH≥7.55) is associated with increased mortality in critically ill patients. Contributing mechanisms include volume contraction reduced glomerular filtration rate, hypokalemia, hypochloremia, mineralocorticoid excess, and impaired renal bicarbonate excretion. Common etiologies include vomiting, excess mineralocorticoids, licorice ingestion, loop or thiazide diuretics, calcium-alkali syndrome, and genetic disorders such as Bartter and Gitelman syndromes or cystic fibrosis (Do et al. 2022).

We present two cases of poorly differentiated neuroendocrine carcinoma, in which the initial clinical manifestation was hypokalemic metabolic alkalosis, later attributed to ectopic ACTH syndrome (EAS). Notably, both patients lacked overt systemic signs of Cushing's syndrome at presentation.

## Case 1

A 71-year-old woman presented to the emergency department with a three-month history of progressive lower extremity weakness, difficulty walking, and elevated blood pressure. Her medical history included long-standing hypertension, atrial fibrillation, peripheral artery disease, and newly diagnosed diabetes mellitus. Current medications were rivaroxaban 20 mg, valsartan/amlodipine 160/10 mg, metformin 1000 mg twice daily, spironolactone 25 mg, insulin glargine 12 units daily, and insulin aspart three times daily.

On admission, her vital signs showed blood pressure 180/95 mmHg, heart rate 93/min, respiratory rate 16/min, and temperature 36.8 °C. Neurological examination revealed right lower extremity muscle strength of 3/5. Laboratory tests at admission, summarized in Table 1, demonstrated normocytic

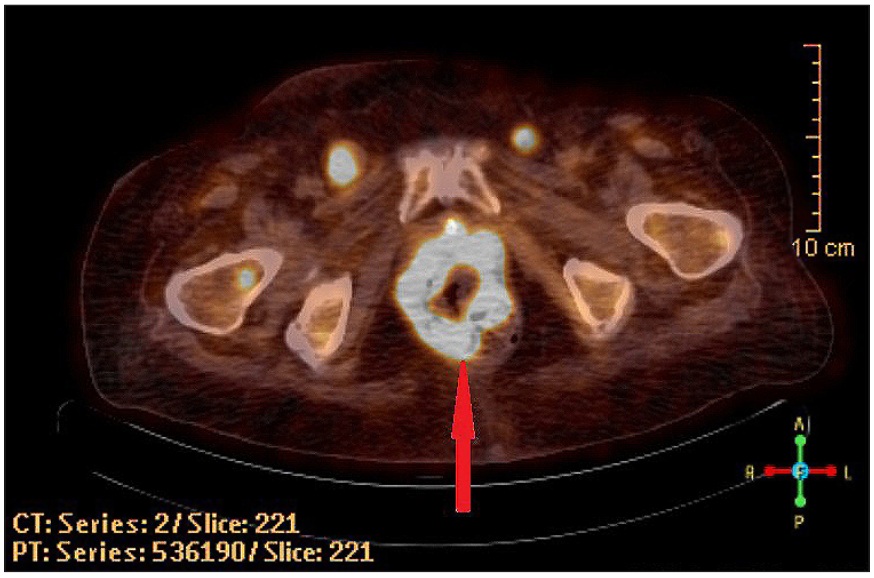


**Figure 1.** Positron emission tomography-computed tomography (PET-CT) of Case 1. The arrow indicates the rectal mass consistent with poorly differentiated neuroendocrine carcinoma. Additional findings include extensive lymphadenopathy and skeletal metastases.

anemia, lymphopenia, neutrophilia, and severe hypokalemia (1.8 mmol/L). Arterial blood gas showed pH 7.51, $pCO_2$ 40.7 mmHg, $HCO_3^-$ 31.6 mmol/L, consistent with metabolic alkalosis.

Further diagnostic evaluation, presented in Table 2, revealed elevated 24-h urinary free cortisol (990 μg/24 h), elevated plasma ACTH (396.2 ng/L), and lack of suppression on low-dose dexamethasone suppression testing (serum cortisol 78.9 μg/dL). Pituitary MRI was normal.

Colonoscopy performed for anemia work-up revealed an ulcerovegetative mass extending 5–6 cm from the anal verge. Biopsy showed poorly differentiated carcinoma with focal synaptophysin staining and high proliferative activity (Ki-67 index 90%) consistent with neuroendocrine differentiation. PET-CT revealed intense uptake in the rectal mass extensive intrathoracic and intraabdominal lymphadenopathy and widespread skeletal metastases (Figure 1).

Based on these findings, hypokalemic metabolic alkalosis was attributed to EAS secondary to poorly differentiated rectal neuroendocrine carcinoma. Despite supportive care, the patient developed multi-organ failure and died in hospital on day 14.

## Case 2

A 67-year-old woman with a history of hypertension presented with progressive fatigue, weakness, and unintentional weight loss over one month. Her only chronic medication was candesartan 16 mg daily.

On admission, vital signs showed blood pressure 165/65 mmHg, heart rate 79/min, respiratory rate 21/min, and temperature 36.2 °C. Physical examination was otherwise unremarkable. Laboratory tests revealed hypokalemia (2.8 mmol/L), renal dysfunction, elevated liver enzymes, lymphopenia, neutrophilia, and elevated ferritin, lactate dehydrogenase (LDH), and vitamin B12 (Table 1). Arterial blood gas showed pH 7.58, $pCO_2$ 37.8 mmHg, $HCO_3^-$ 34.7 mmol/L, consistent with metabolic alkalosis.

Further testing, as shown in Table 2, revealed elevated urinary chloride (43 mEq/L), elevated 24-h urinary free cortisol (1716 μg/24 h), elevated plasma ACTH (83.98 ng/L), and lack of suppression on low-dose dexamethasone suppression testing (cortisol 92 μg/dL). In addition, tumor markers CEA and CA 19-9 were elevated. Pituitary MRI was normal.

Chest CT demonstrated a 38-mm right hilar mass (Figure 2). Bronchoscopy revealed tumor infiltration in the right upper lobe bronchus, and biopsy showed

**Table 1**
Laboratory findings at hospital admission

| Parameter | Case 1 | Case 2 | Reference range |
|---|---|---|---|
| Complete blood count (CBC) | | | |
| White blood cell (10^3/μL) | **10.6** | **15.4** | 4–10 |
| Hemoglobin (g/dL) | **9.7** | 14.9 | 12–16 |
| MCV (fL) | 84.8 | 90.8 | 80–100 |
| Platelet (10^3/μL) | 150 | 182 | 100–400 |
| Neutrophils (10^3/μL) | **9.49** | **14.65** | 2–7 |
| Lymphocytes (10^3/μL) | **0.6** | **0.3** | 0.8–4.0 |
| Biochemical analyses | | | |
| Fasting glucose (mg/dl) | 119 | 131 | 74–106 |
| Urea (mg/dl) | **52** | **94** | 16.6–48.5 |
| Creatinine (mg/dl) | 0.75 | **1.44** | 0.5–0.9 |
| Uric acid (mg/dl) | 5.3 | **7.8** | 2.4–5.7 |
| AST (U/L) | 18 | **120** | 0–32 |
| ALT (U/L) | 19 | **267** | 0–33 |
| GGT (U/L) | 23 | **920** | 0–40 |
| ALP (U/L) | 98 | **181** | 35–104 |
| Total bilirubin (mg/dL) | 0.62 | **1.59** | 0–1.2 |
| Direct bilirubin (mg/dL) | 0,28 | **0.83** | 0–0.3 |
| LDH (U/L) | **280** | **528** | 135–214 |
| Total protein (g/L) | **46.2** | 67.5 | 66–87 |
| Albumin (g/L) | **26.7** | 36.6 | 35–52 |
| Sodium (mmol/L) | 145 | 140 | 136–145 |
| Potassium (mmol/L) | **1.8** | **2.8** | 3.5–5.1 |
| Calcium (mg/dL) | 9.38 | 9.17 | 8.8–10.2 |
| Magnesium (mg/dL) | 1.85 | 2.50 | 1.6–2.4 |
| C-reactive protein (mg/L) | **24.11** | 4.72 | 0–5 |
| Ferritin (μg/L) | **984** | **263** | 13–150 |
| Vitamin B12 (ng/L) | **1117** | **1537** | 197–771 |
| ELISA tests | | | |
| HBsAg | Negative | Negative | |
| Anti-HCV | Negative | Negative | |
| Anti-HIV | Negative | Negative | |
| Coagulation tests | | | |
| INR | **1.79** | 1.01 | 0.8–1.2 |
| aPTT (sn) | 27.3 | 15.7 | 21–35 |

Bold values indicate results outside the reference range. Abbreviations: ALP – alkaline phosphatase; ALT – alanine aminotransferase; aPTT – activated partial thromboplastin time; AST – aspartate aminotransferase; GGT – gamma glutamyl transferase; INR – international normalized ratio; LDH – lactate dehydrogenase; MCV – mean corpuscular volume.

high-grade small-cell neuroendocrine carcinoma. Immunohistochemistry revealed focal synaptophysin staining, diffuse positivity for CD56 and TTF-1, and Ki-67 index >90%. PET-CT confirmed a hypermetabolic right hilar tumor with widespread lymph node, bone, and hepatic metastases.

The diagnosis of hypokalemic metabolic alkalosis secondary to EAS due to high-grade small-cell neuroendocrine carcinoma was established. The patient was referred to oncology and started on carboplatin and etoposide. However, she developed rapid progression with multi-organ failure and died in the intensive care unit during the third day of chemotherapy.

## Discussion

Ectopic ACTH syndrome (EAS) is a form of Cushing's syndrome caused by excessive production of ACTH by non-pituitary tumors. In this condition, elevated ACTH levels stimulate excessive cortisol secretion from the adrenal glands leading to clinical findings of hypercortisolism. Typical clinical presentations of EAS include rapidly progressive weakness, severe hypokalemia, myasthenia, and serious infections. One of the most common causes of ectopic ACTH production are NETs. The NETs most frequently associated with EAS are pulmonary or thymic neoplasms, pancreatic NETs, pheochromocytoma, and medullary thyroid carcinoma (Rizen and Phan 2022; Gadelha et al. 2023).

**Table 2**
Results of further diagnostic evaluation

| Parameter | Case 1 | Case 2 | Reference range |
|---|---|---|---|
| Hormonal tests | | | |
| Cortisol (μg/dL) | **71.3** | **115** | 06.00–10.00: 4.82–19.5 |
| ACTH (ng/L) | **396.2** | **83.98** | 7.2–63.3 |
| Aldosterone (ng/dL) | **0.07** | 8.26 | 2.21–35.3 |
| Plasma renin activity (ng/mL/h) | 0.12 | 0.351 | <4.95 |
| Free cortisol (24-h urine) (μg/24 h) | **990** | **1716** | <45 |
| Dexamethasone suppression test (1 mg) (μg/dL) | **78.9** | **92** | <2 |
| Tumor markers | | | |
| CEA (μg/L) | **102** | **57.4** | 0–5 |
| CA-19.9 (U/mL) | **750** | **601** | 0–34 |
| CA-15.3 (U/mL) | 18.1 | **73.1** | 0–26.2 |
| CEA-125 (U/mL) | **58.8** | 20.8 | 0–35 |
| AFP (μg/L) | <1 | 2.67 | 0–7 |

Bold values indicate results outside the reference range. Abbreviations: ACTH – adrenocorticotropic hormone; AFP – alpha-fetoprotein; CEA – carcinoembryonic antigen; CA 19-9 – carbohydrate antigen 19-9; CA 15-3 – cancer antigen 15-3; CA 125 – cancer antigen 125.

In a retrospective population-based cohort study including 73,782 cases aged ≥18 years diagnosed with NETs. The most frequent primary tumor sites were lung/bronchus (30.6%), followed by small intestine (22.2%), rectum (16.2%), colon (13.4%), pancreas (10.8%), and stomach (6.8%). Median survival time was 41 months and overall survival rates at 1, 3, 5, and 10 years were 72.8%, 52.7%, 39.4%, and 18.1%, respectively. In that study, primary tumor site was reported as one of the strongest prognostic indicators with the best prognosis in rectal NETs and the worst in pancreatic NETs (Yan et al. 2022).

On the other hand, the presence of EAS has been reported to negatively affect prognosis in NET patients. In a large study conducted by Kamp et al. (2016), EAS was detected in 32 of 918 NET patients (3.2%) most commonly due to thoracic and pancreatic NETs. Median overall survival was 61.2 months in non-EAS patients and 41.4 months in EAS patients. Five-year survival was significantly shorter in EAS compared with non-EAS patients.

In this case series, we are discussing two patients who presented without overt systemic symptoms or signs suggestive of malignancy or Cushing's syndrome, but with resistant hypokalemia and metabolic alkalosis and were later diagnosed with advanced-stage neuroendocrine carcinoma causing EAS. Both patients had widespread metastatic disease at diagnosis and died due to multiple organ failure. In both cases, the main clinical clue at hospital admission was hypokalemic metabolic alkalosis and the initial differential diagnosis focused on this finding.

Hypokalemic metabolic alkalosis can be classified based on the blood pressure levels as low or high blood pressure types or according to urinary chloride as chloride-responsive (<20 mEq) and chloride-unresponsive (>20 mEq) forms (Do et al. 2022). Low blood pressure etiologies include genetic (Bartter syndrome, Gitelman syndrome, autosomal dominant hypocalcemia with hypercalciuria) and acquired disorders (e.g., diuretic use, vomiting), while high blood pressure etiologies include genetic (Liddle syndrome, 11β-hydroxylase deficiency) and acquired conditions (primary or secondary hyperaldosteronism, Cushing's syndrome, chronic corticosteroid administration, licorice abuse). In our cases, given the advanced age, presence of hypertension and absence of diuretic use or vomiting,

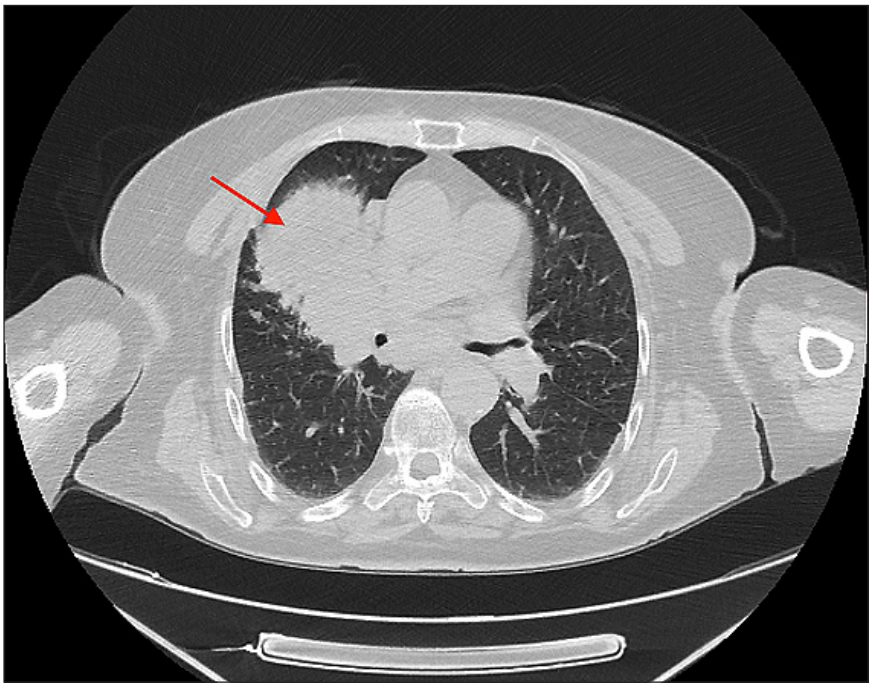

**Figure 2.** Thoracic computed tomography (CT) of Case 2. The arrow indicates the right hilar mass consistent with small-cell neuroendocrine carcinoma.

and low blood pressure etiologies were excluded. Similarly, advanced age, lack of resistant hypertension, and normal aldosterone and renin levels made genetic high blood pressure etiologies such as Liddle syndrome and 11β-hydroxysteroid dehydrogenase inactivating mutations unlikely. Furthermore, normal serum aldosterone and plasma renin activity along with unremarkable adrenal imaging ruled out primary and secondary hyperaldosteronism. No history of licorice intake or exogenous corticosteroid use was reported.

Regarding Cushing's syndrome, our patients had elevated 24-h urinary free cortisol and plasma ACTH levels, failure of cortisol suppression with low-dose dexamethasone suppression test, and no adrenal pathology on imaging suggesting ACTH-dependent Cushing's syndrome. Although inferior petrosal sinus sampling (IPSS), the gold standard for differentiating pituitary from ectopic ACTH production, was unavailable in our center, the absence of pituitary lesions on MRI supported a diagnosis of EAS.

For tumor localization, in the first case, colonoscopy performed for anemia revealed a rectal mass and biopsy confirmed rectal neuroendocrine carcinoma. In the second case, chest CT revealed a thoracic mass and bronchoscopic biopsy confirmed small-cell neuroendocrine carcinoma as the cause of EAS.

Neuroendocrine neoplasms are classified according to genetic, morphologic and clinical features as well-differentiated NETs (NET G1, G2, G3) or poorly differentiated neuroendocrine carcinomas (small-cell or large-cell carcinoma). This classification is based on morphology, mitotic index, and immunohistochemical markers such as synaptophysin, chromogranin, and Ki-67 (Rindi et al. 2022). In both of our cases, immunohistochemical analysis (focal synaptophysin positivity, Ki-67 >90% and small-cell cytomorphology) confirmed poorly differentiated neuroendocrine carcinoma. At diagnosis, both patients had widespread metastatic disease-causing multi-organ dysfunction. Additionally, the coexistence of EAS leading to hypokalemic metabolic alkalosis likely contributed to both the clinical presentation at admission and the rapid aggressive disease course observed.

## Acknowledgement

The authors thank the staff of Istanbul Medeniyet University, Faculty of Medicine, Prof. Dr. Suleyman Yalcin City Hospital for their clinical support in patient management.

***Conflict of interest:*** *The authors declare no conflict of interest.*

## References

Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, Shih T, Yao JC. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. JAMA Oncol 1, 1335–1342, 2017.

Do C, Vasquez PC, Soleimani M. Metabolic alkalosis pathogenesis, diagnosis, and treatment: Core curriculum 2022. Am J Kidney Dis 80, 536–551, 2022.

Gadelha M, Gatto F, Wildemberg LE, Fleseriu M. Cushing's syndrome. Lancet 402, 2237–2252, 2023.

Kamp K, Alwani RA, Korpershoek E, Franssen GJ, de Herder WW, Feelders RA. Prevalence and clinical features of the ectopic ACTH syndrome in patients with gastroenteropancreatic and thoracic neuroendocrine tumors. Eur J Endocrinol 174, 271–280, 2016.

Rindi G, Mete O, Uccella S, Basturk O, La Rosa S, Brosens LAA, Ezzat S, de Herder WW, Klimstra DS, Papotti M, Asa SL. Overview of the 2022 WHO classification of neuroendocrine neoplasms. Endocr Pathol 33, 115–154, 2022.

Rizen EN, Phan AT. Neuroendocrine tumors: a relevant clinical update. Curr Oncol Rep 24, 703–714, 2022.

White BE, Rous B, Chandrakumaran K, Wong K, Bouvier C, Van Hemelrijck M, George G, Russell B, Srirajaskanthan R, Ramage JK. Incidence and survival of neuroendocrine neoplasia in England 1995–2018: A retrospective, population-based study. Lancet Reg Health Eur 23, 100510, 2022.

Yan L, Xu Y, Pan J, Bai J, Long Q, He N, Hu P, Liu M, Ji H, Li X, Tang Q. Prognostic evaluation of patients with rectal neuroendocrine neoplasms and hepatic metastases: A SEER database Analysis. J Oncol 2022, 2451282, 2022.