Ukrainian Journal of Nephrology and Dialysis
Scientific and Practical, Medical Journal

Founder:
- National Kidney Foundation of Ukraine

ISSN 2304-0238;
eISSN 2616-7352

Journal homepage: https://ukrjnd.com.ua

Clinical case reports

doi: 10.31450/ukrjnd.1(81).2024.01

Esra Geçgel[1], Alper Alp[2], Emel Kılıçarslan Karpuzoğlu[3], Dilek Gibyeli Genek[2], Bülent Huddam[2]

Uncommon presentation of small cell lung carcinoma with ectopic adrenocorticotropic hormone secretion and resistant hypokalemia: A case report

[1]Department of Internal Medicine, Faculty of Medicine, Mugla Sıtkı Koçman University, Mugla, Turkey
[2]Department of Nephrology, Faculty of Medicine, Mugla Sıtkı Koçman University, Mugla, Turkey
[3]Department of Pathology, Faculty of Medicine, Pamukkkale University, Denizli, Turkey

Citation: Geçgel E, Alp A, Karpuzoğlu EK, Genek D.G, Huddam B. Uncommon presentation of small cell lung carcinoma with ectopic edrenocorticotrophic hormone secretion and resistant hypokalemia: A case report. Ukr J Nephr Dial. 2024;1(81):3-9. doi: 10.31450/ukrjnd.1(81).2024.01.

Abstract. *Paraneoplastic syndromes can serve as initial indicators of malignancy, with small cell lung cancer accounting for 13% of new lung cancer diagnoses. The most prevalent paraneoplastic syndrome associated with small cell lung cancer is inappropriate antidiuretic hormone syndrome, followed by ectopic adrenocorticotropic hormone-mediated Cushing's syndrome. Cushing's syndrome manifests as hypercortisolemia and presents with diverse symptoms, including central obesity, plethora, menstrual irregularities, hypertension/diabetes mellitus, ecchymoses, osteoporosis, muscle weakness, virilization/hirsutism, skin atrophy, decreased libido, and infertility. This case report details the uncommon presentation of small cell lung carcinoma manifesting with ectopic adrenocorticotropic hormone secretion (EAS), leading to resistant hypokalemia and rhabdomyolysis. This case emphasizes the importance of considering EAS in severe cases of Cushing's syndrome and highlights the diagnostic and therapeutic challenges associated with this condition.*

Key words: *small cell lung cancer, Cushing's syndrome, hypokalemia.*

Article history:
Received November 17, 2023
Received in revised form December 02, 2023
Accepted December 05, 2023

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

Correspondence should be addressed to Alper Alp: alperalp@mu.edu.tr

УДК: 616.24-006.6-07

Есра Гечгель[1], Альпер Альп[2], Емель Кілічарслан Карпузоглу[3], Ділек Гіб'єлі Генек[2], Бюлент Худдам[2]

Рідкісна презентація дрібноклітинної карциноми легені з ектопічною секрецією адренокортикотропного гормону та резистентною гіпокаліємією: клінічний випадок

[1]Кафедра внутрішньої медицини, медичний факультет, Університет Мугла Сіткі Кочмана, Мугла, Туреччина
[2]Кафедра нефрології, медичний факультет, Університет Мугла Сіткі Кочмана, Мугла, Туреччина
[3]Кафедра патології, медичний факультет, Університет Памуккале, Денізлі, Туреччина

Резюме. *Паранеопластичний синдром може бути першим клінічним проявом злоякісного захворювання, де дрібноклітинний рак легенів становить близько 13% нових випадків раку легенів. Найпоширенішим паранеопластичним синдромом, пов'язаним з дрібноклітинним раком легені, є синдром порушення секреції антидіуретичного гормону, за яким слідує синдром Кушинга. Синдром Кушинга обумовлений гіперкортизолемією та проявляється різними симптомами, включаючи центральне ожиріння, повнокров'я, порушення менструального циклу, гіпертензію, цукровий діабет, екхімози, остеопороз, м'язову слабкість, гірсутизм, атрофію шкіри, зниження лібідо та безпліддя. Цей клінічний випадок демонструє рідкісні прояви дрібноклітинної карциноми легенів, обумовлені ектопічною секрецією адренокортикотропного гормону (ЕСАКТГ), що призвело до резистентної гіпокаліємії та рабдоміолізу. Цей випадок підкреслює важливість розгляду ЕСАКТГ у важких випадках синдрому Кушинга та підкреслює діагностичні та терапевтичні проблеми, асоційовані з цим станом.*

Ключові слова: *дрібноклітинний рак легені, синдром Кушинга, гіпокаліємія.*

Introduction. Cushing's syndrome (CS) is classified as; adrenocorticotropic hormone (ACTH)-dependent CS and ACTH-independent CS and Pseudo-Cushing's syndrome. Only approximately 10% are caused by entities that cause ectopic ACTH release, mostly malignant. Ectopic ACTH syndrome (EAS) is caused by abnormal expression of the proopiomelanocortin gene product arising from non–pituitary tumors in response to ectopic activation of the pituitary-specific promoter of this gene [1]. EAS involves ACTH secretions from a region other than the pituitary gland, especially from the tumoral tissue, leading to high ACTH, cortisol, and aldosterone levels, as well as, accordingly, refractory hypokalemia, metabolic alkalosis, and hypertension, which can be the case with paraneoplastic syndromes (PNS). Ectopic ACTH secretion should be suspected in severe cases of CS, often due to an underlying malignancy, most commonly Small cell lung cancer (SCLC) or neuroendocrine tumors of pulmonary origin, and rarely thymus or endocrine pancreas. Thorax computed tomography (CT) should be the first choice as the initial imaging modality in cases where ectopic ACTH secretion is suspected, because the origin of most ACTH-producing tumors is the intrathoracic area. Another important complication that may develop in severely hypokalemic patients is rhabdomyolysis. In this case, we present our diagnostic approach to a patient presenting with various metabolic abnormalities.

Case report. A 56-year-old male patient presented to the emergency department with complaints of shortness of breath, coughing, and weakness. His medical history included arterial hypertension, which was diagnosed 2 weeks prior, and a history of 30-pack-year smoking. As an antihypertensive he had been using 150 mg irbesartan+12.5 mg hydrochlorothiazide. His family history was noncontributory. Upon a physical examination, he had a plethoric facial appearance. Arterial blood pressure was 165/99 mmHg, temperature 36.5 °C, HR 80/min, and saturation was 90%, and there was widespread muscle pain and weakness in his body. Rales were present in the lung bases. The laboratory values on admission are shown in Table 1.

Alper Alp
alperalp@mu.edu.tr

Table 1

Initial Laboratory Tests upon Admission.

Urea (mg/dL)	47	White blood cells	13.000	pH	7.77
Creatinine (mg/dL)	0.97	Neutrophil	11.320	pCO_2 (mmHg)	54
Sodium (mmol/L)	136	Lymphocyte	1.050	Bicarbonate (mEq/L)	60
Potassium (mmol/L)	1.45	Monocytes	490	Lactate (U/L)	1.9
Calcium (mg/dL) (corrected)	8.45	Hemoglobin (gr/dL)	12.1	Lactate dehydrogenase (U/L)	1.514
Albumin (gr/L)	32	Hematocrit (%)	38.4	Creatine kinase (U/L)	12.240
Uric acid (mg/dL)	5.7	Mean corpuscular volume (fL)	85	C-reactive protein (mg/L)	23.63
Alanine aminotransferase (U/L)	308	Phosphorus (mg/dL)	2.75	Myoglobin (ng/mL)	3.000
Aspartate aminotransferase (U/L)	456	Platelet (mm^3)	155.000	Magnesium (mg/dL)	2.17

T flattening was observed on electrocardiography possibly due to severe hypokalemia, and potassium citrate+potassium bicarbonate oral tablets, spironolactone tablets, and intravenous potassium were initiated at optimal doses. Thiazide was discontinued and irbesartan was given at 300 mg as the patient was hypertensive during the follow up (170–180/85–90 mmHg). Further, an intravascular saline infusion was started due to very high levels of creatinine kinase and myoglobin. Although potassium replacement was performed at maximum dosage, we could not succeed a definite biochemical response. The follow-up laboratory values are shown in Table 2.

Table 2

Potassium levels and blood gas analysis results during follow-up

	On admission	2nd day	3rd day
Potassium (mmol/L)	1.45	1.70	1.88
pH	7.77	7.69	7.64
Bicarbonate (mEq/L)	60	60	56
Creatine kinase (U/L)	12.240	6.876	2.568

Lung X-ray revealed an approximately 1×1.5-cm-sized irregular, heterogeneous increased density at right lung, near the 4th costa and costochondral joint level, while fullness in the right hilar region was noticeable. Considering there may be EAS in the etiology of hypokalemia in the patient, whose resistant hypokalemia persisted despite optimal treatment doses, thorax CT was performed. ACTH, renin, aldosterone, and cortisol levels were 150.1 pg/ml (7.2–63.3 pg/mL), 0.89 ng/mL/s (0.2–3.4 ng/mL/h), 14.53 ng/dL (1–21 ng/dL), and 63.44 µg/dL (5–20 µg/dL), respectively. Thorax CT revealed: pathological lymphadenopathies, the largest of which was 42×33 mm, were observed in the paratracheal, paraaortic, and subcarinal areas, as were a mass image measuring about 4×2.5 cm in the right hilar and multiple nodules in the bilateral lung parenchyma (Fig. 1).

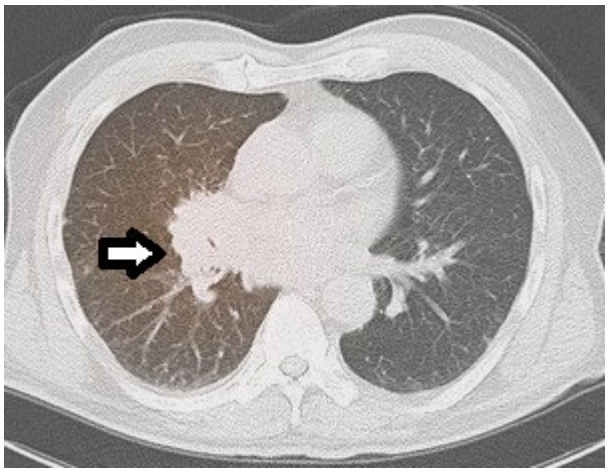

Figure 1. Thorax CT. A mass image in the right hilar region.

ACTH-dependent CS related to lung pathology was considered. Upon a bronchoscopic biopsy, small cell lung carcinoma with CD56 (+0), thyroid transcription factor-TTF-1 (+), dot-like pan-cytokeratin (PANCK) [+], p40 [-], vimentin [-], and high proliferation index of KI-67 (98%) were detected immunohistochemically (Fig. 2).

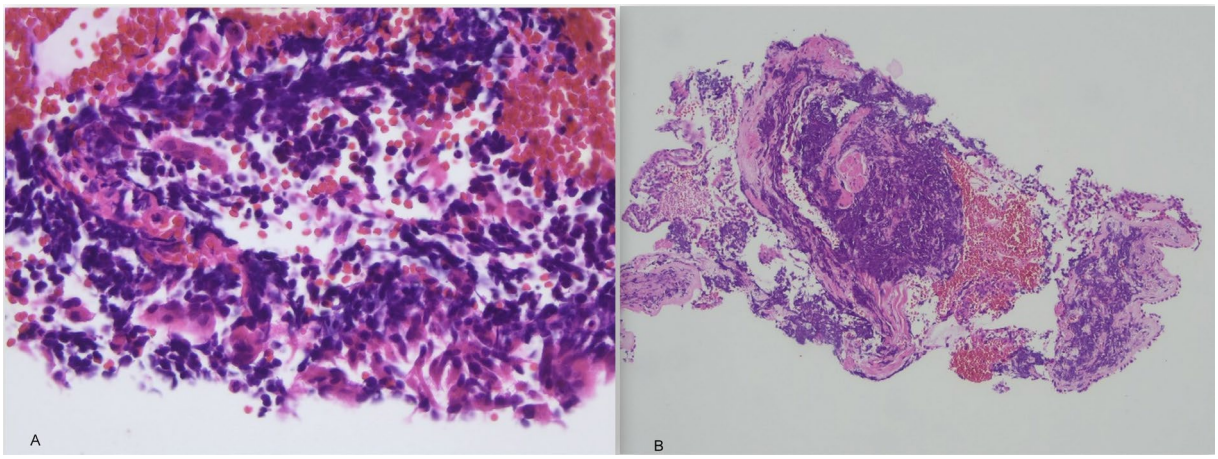

Fig. 2. Histopathological assessment of the hilar mass.

2A: Malignant tumoral proliferation consisting of small cells with crushed artifacts, forming infiltrative islands in loose connective tissue containing smooth muscle, under pseudostratified ciliated epithelium in a single row on the surface and in some shed areas. (4x magnification, HE)

2B: At high magnification (40x), tumor cells are small cells with hyperchromatic nuclei, and pleomorphic, narrow cytoplasm.

SCLC presenting with paraneoplastic syndrome, EAS, associated with severe hypokalemia-related rhabdomyolysis was the diagnosis. However, the patient, who was followed up in the intensive care unit due to hypoxemia in the post-bronchoscopy period, was lost during intensive care follow-up. During this period, maximal pulmonary rehabilitation support, appropriate intravenous antibiotic therapy, and electrolyte replacement were provided, but the patient's clinical deterioration was very rapid. There was not enough time to prepare the patient for surgery and the opportunity to provide rapid medical treatment.

Discussion. The most common etiologies of endogenous CS are a pituitary ACTH-secreting adenoma (Cushing's disease) in 60–70% of patients and primary adrenal CS in 20–25%. The remaining 5–10% of cases represent ectopic CS and are the result of paraneoplastic ectopic ACTH (mostly) and less likely corticotropin-releasing hormone secretion. All cancer types that show neuroendocrine differentiation have the potential to develop EAS. The most prevalent tumors associated with ectopic CS are SCLC of the lung and pulmonary carcinoid tumors. Also, pancreatic and thymic neuroendocrine tumors, breast carcinoma, medullary thyroid cancer, pheochromocytoma, gastric cancer, and cervical cancer can be considered as the other causes.

EAS is a heterogeneous, rare condition with a reported incidence of 1.4 new cases per 10 million inhabitants per year [2]. Hypercortisolism is usually severe, patients often have a short course of the disease and a rapid progression of symptoms due to high serum ACTH and cortisol status. The typical manifestations of CS may be obscure, and patients may be under investigation for secondary hypertension, hypokalaemic metabolic alkalosis, and/or hyperglycemia. It may also be associated with typical features of intense proximal muscle weakness, hyperpigmentation, and edema [3].

In clinical practice, hypokalemia often occurs due to the use of diuretics (especially thiazides), antipsychotics, and laxatives, as well as secondary to alkalosis, vomiting, diarrhea, elevated insulin, and hypercortisolism/mineralocortisolism or CS, including ectopic ACTH secretion. Gastrointestinal loss, primary or secondary hyperaldosteronism, hypomagnesemia, renal tubular acidosis, diabetic ketoacidosis, and Liddle, Bartter, and Gitelman syndromes are also some of the main reasons of hypokalaemia. Our patient had recently been started on thiazide therapy, which probably potentiated hypokalemia.

The presence of hypokalemia in a patient with arterial hypertension first brings to mind primary hyperaldosteronism. Considering the mineralocorticoid effect of high cortisol concentrations, other causes should not be overlooked. Under normal conditions, the mineralocorticoid effect of cortisol is not prominent due to its local conversion to cortisone by the action of 11β-hydroxysteroid dehydrogenase (rate-limiting step in the mineralocorticoid action of cortisol). When plasma concentrations of cortisol are very high, the enzyme is saturated so that the action of this enzyme is insufficient, and mineralocorticoid effects appear (cortisol binding to mineralocorticoid receptors to produce effects similar to that of aldosterone), leading to hypertension and hypokalemia through the renin–angiotensin–aldosterone system (RAAS). It is through indirect overactivation of this system (activated by the ACTH)

that patients with CS develop hypokalemia. Due to the increased aldosterone, the Na^+-K^+-ATPase pump is activated, and the absorption of Na^+ and water in the distal tubules and K^+ secretion increase. In addition, K^+ and HCO3- secretions increase with the activation of the H-K^+ ATPase pump in the apical membrane of intercalated cells in the cortical and external medullary collecting ducts. Due to all these mechanisms, resistant hypokalemia, metabolic alkalosis, and hypertension occur in EAS.

Under physiological conditions, the release of potassium from the muscles causes vasodilation. Therefore, blood flow toward the muscles increases. Further, under deep hypokalemic conditions (K^+<2.5 mEq/L), intracellular calcium levels increase due to dysfunction in the Na^+-K^+ ATPase and Ca-Na^+ channels, where mitochondrial dysfunction and cell destruction occur due to ATP depletion, leading to rhabdomyolysis. Rhabdomyolysis in EAS is rare, but almost always is associated with severe hypokalemia. A similar case with deep hypokalemia and secondary rhabdomyolysis was identified in the report of Wei Qiang et al. Although chemotherapy was started in this case, survival was limited to only 1 month [4]. Rhabdomyolysis risk increases when potassium levels drop below 2-2.5 mmol/mL [5]. When severe hypokalemia is detected, we should be aware of the possibility of rhabdomyolysis development. Effective regression of creatinine kinase levels was achieved with intravascular hydration therapy in our patient.

Compared to pituitary-dependent Cushing's disease, EAS is more strongly associated with biochemical abnormalities (especially electrolyte disturbances) and less with the classic physical manifestations of CS. This is due to much higher concentrations of ACTH and cortisol in the EAS [6]. Additionally, patients die before they have a physical Cushingoid appearance. In our patient, also, no specific physical examination findings other than the plethoric facial appearance were prominent in terms of CS.

Patients with EAS almost always have hypertension, but the frequency of hypokalemia may vary. Espinosa-de-Los-Monteros et al, reported that hypertension were present in 92.8% of the cases, in this regard, the prevalence of hypokalemia among patients with EAS was 42.8% [7]. In another study that retrospectively analyzed EAS patients; most of the primary tumors were located in the thorax (57.1%), the most common associated comorbidity was hypertension in 93%. In 92.3% of the patients mean potassium level was 2.3 mEq/L. 50% of patients required oral+intravenous potassium replacement to manage hypokalemia. The prognosis was poor for the patients with intrathoracic lesions (75% of the cases died) [8]. In another study; hypokalemia was so frequent among patients with EAS (85.7%). The median potassium was 2.6 meq/l (1.2-3.9 meq/l). A median of 5 days (1–20) required for correction for hypokalemia. All patients required parenteral potassium, in addition to oral potassium+spironolactone. Metabolic alkalosis was seen in 17/21 (80%) patients. Hypokalemia was rare in patients with pituitary-dependent CS [9]. According to Montserrat et al. in a study where they analyzed the incidence of paraneoplastic syndrome and endocrine-metabolic pathologies, the incidence of hypokalemia in PNS in the study was 0.71 (1,000 people/year) [10].

EAS developed at a rate of 1–5% in cases diagnosed with SCLC [11, 12]. Tumor histopathology and high cortisol concentration are the two most important points in terms of prognosis in EAS patients. The presence of EAS due to a poor response to chemotherapy, increased risk of infection, and increased risk of venous thromboembolism in SCLC with ectopic CS is a poor prognosis indicator, with 5-year survival in EAS that develops during the course of SCLC being <7% [13]. The median survival without treatment for SCLC was shown to be 6.8 months on average, and the median survival with treatment was 9.3 months. Unfortunately, average life expectancy of SCLC with ectopic CS is 3–5 months, regardless of the treatment process [14, 15].

Different treatment approaches can be seen in similar cases in the literature. Unfortunately, the overall survival rate is low. In the article by Richa et al. presenting 3 cases (2 cases of small cell lung cancer, one case of neuroendocrine tumor of unknown etiology), in addition to standard treatments, one case included ketokenazole+doxorubicin+paclitaxel, ketoconazole+chemotherapy in one case, and somatostatin and everolimus treatments in addition to carboplatin and etoposide were given in the other, but the patients died within 1 year at the latest [16]. Zhang et al. successfully used CT-guided radiofrequency ablation in the diagnosis of lung carcinoid tumor and control of hypercortisolism in a surgically difficult case that was unresponsive to drug therapy [17]. In Suyama et al.'s case, EAS developed in a patient receiving chemotherapy treatment for small cell lung cancer and a good response was obtained to mitotane treatment in terms of clinical and cortisol level reduction [18]. In a case reported by Braun et al., an improvement in metabolic abnormalities was observed within 2 weeks after cisplatin in a patient with EAS associated with small cell lung cancer [19]. In a similar case by Ferreira et al., effective clinical improvement was achieved in the short term with metyrapone and the patient was referred to the oncology unit for carboplatin + etoposide treatment [20].

The main goal in the EAS treatment approach is curative surgical resection. Medical treatment is used in the following cases: contraindication to surgery or preoperative preparation phase, postoperative hypercortisolism status (relapse/insufficient surgery), CS treatment in non-localizable tumors [21]. Alba et al.'s algorithmic treatment approach on this issue is up-to-date and comprehensive. Primary medical treatment primarily includes stabilization of comorbid clinical conditions, which includes the control of hypertension, blood glucose and hypokalemia, thromboembolism and infection prophylaxis, and the use of drugs that reduce

cortisol levels (ketokenazole and its enantiomer, levoketokenazole; metyrapone, a potent 11β-hydroxylase inhibitor and a partial 18-hydroxylase inhibitor; osilodrostat, a rapid-acting 11β-hydroxylase inhibitor; mifepristone, an antiprogesterone and glucocorticoid receptor blocking agent; and etomidate) [22]. The most commonly used steroidogenesis inhibitor in clinical practice is ketoconazole, a drug that inhibits multiple cytochrome P450 steroidogenic enzymes. When using all these drugs, attention should be paid to CYP3A4 inhibition and induction. Etomidate is a drug that can be used intravenously, provides acute cortisol control and inhibits 11β-hydroxylase and 20, 22 desmolase. Frequent monitoring of cortisol levels is required to achieve targeted low serum and urine cortisol levels during medical treatment [23]. In cases where the tumor cannot be resected, other treatment options are; somatostatin analogues (octreotide and lanreotide), everolimus, capecitabine and temozolomide, tyrosine kinase inhibitors (vandetanib, sorafenib or sunitinib), radiofrequency ablation, transarterial chemoembolization/radioembolization [22].

Further, 70–85% of malignancies in the thoracic region may lead to EAS [24]. Early diagnosis and localization of the ectopic source of ACTH is the main point of the approach. For this reason, thoracic CT should definitely be performed in patients with resistant hypokalemia, severe metabolic alkalosis, a Cushingoid appearance (though it may be absent), and, especially, newly developed hypertension. If EAS clinic is present or there is a high diagnostic suspicion, it has been recommended to use a neck-to-pelvis thin-slice CT scan or MRI to provide tumor localization. Modalities such as octreotide scan or positron emission tomography (PET)-CT have been recommended for further and detailed examination [25].

Conclusions. Early diagnosis of EAS is based on clinical suspicion and rapid evaluation. Different clinical entities may underlie serious and treatment-resistant metabolic disorders.

Funding. The authors did not receive any financial support from any organization for the paper submitted.

Data availability. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication. The parent of the patients has provided written consent for the publication of this case report, and the authors received informed consent as part of the submission process.

Competing interests. The authors declare that they have no competing interests.

Authors' contributions.

Esra Geçgel and Alper Alp: the manuscript writing and made significant contributions to its content.

Esra Geçgel and Emel Karpuzoğlu: data collection;

Dilek Gibyeli Genek and ***Bülent Huddam:*** the manuscript revision; All authors read and approved the manuscript.

References:

1. *Ye L, Li X, Kong X, Wang W, Bi Y, Hu L, et al.* Hypomethylation in the promoter region of POMC gene correlates with ectopic overexpression in thymic carcinoids. J Endocrinol. 2005; 185(2):337–343. doi: 10.1677/joe.1.05963.
2. *Young J, Haissaguerre M, Viera-Pinto O, Chabre O, Baudin E, Tabarin A.* Cushing's s ndrome due to ectopic ACTH secretion: an expert operational opinion. Eur J Endocrinol. 2020;182:R29-R58. doi: 10.1530/EJE-19-0877.
3. *Rodrigues P, Castedo JL, Damasceno M, Carvalho D.* Ectopic Cushing's syndrome caused by a pulmonary ACTH-secreting tumor in a patient treated with octreotide. Arq Bras Endocrinol Metabol. 2012;56(7):461-464. doi: 10.1590/s0004-27302012000700009.
4. *Qiang W, Song S, Chen T, Wang Z, Feng J, Zhang J, et al.* A rare case of ectopic ACTH syndrome with rhabdomyolysis. BMC Endocr Disord. 2021;21(1):98. doi: 10.1186/s12902-021-00755-0.
5. *Zhang Wen, Li Chuanwei, Zeng Chunyu, Hui H, Weimin L.* Rhabdomyolysis presenting with severe hypokalemia in hypertensive patients: a case series BMC Research Notes. 2013; 6:155. doi: 10.1186/1756-0500-6-155.
6. *Isidori AM, Kaltsas GA, Pozza C, Frajese V, Newell-Price J, Reznek RH, et al.* The ectopic adrenocorticotropin syndrome: clinical features, diagnosis, management, and long-term follow-up. J Clin Endocrinol Metab. 2006; 91 (2): 371-377. doi: 10.1210/jc.2005-1542.
7. *Espinosa-de-Los-Monteros AL, Ramírez-Rentería C, Mercado M.* Clinical Heterogeneity of Ectopic ACTH Syndrome: A Long-Term Follow-Up Study. Endocr Pract. 2020; 26(12):1435-1441. doi: 10.4158/EP-2020-0368.
8. *Lopez-Montoya V, Gutierrez-Restrepo J, Grajales JLT, Aristizabal N, Pantoja D, Roman-Gonzalez A, et al.* Ectopic Cushing syndrome in Colombia. Arch Endocrinol Metab. 2021;64(6):687-694. doi: 10.20945/2359-3997000000271.
9. *Sathyakumar S, Paul T, Asha HS, Gnanamuthu BR, Paul MJ, Abraham DT, et al.* ECTOPIC CUSHING SYNDROME:A 10-YEAR EXPERIENCE FROM A TERTIARY CARE CENTER IN SOUTHERN INDIA. Endocr Pract. 2017; 23(8):907–914. doi: 10.4158/EP161677.OR.
10. *Miret M, Horváth-Puhó E, Déruaz-Luyet A, Sørensen HT, Ehrenstein V.* Potential paraneoplastic syndromes and selected autoimmune condi-

tions in patients with non-small cell lung cancer and small cell lung cancer: A population-based cohort study. PLoS One. 2017; 12(8):e0181564. doi: 10.1371/journal.pone.0181564.

11. *Jeong C, Lee J, Ryu S, Lee HY, Shin AY, Kim JS, et al.* A Case of Ectopic Adrenocorticotropic Hormone Syndrome in Small Cell Lung Cancer. Tuberc Respir Dis (Seoul). 2015 Oct;78(4):436-9. doi: 10.4046/trd.2015.78.4.436.
12. *Foray N, Stone T, Johnson A, Ali M, Kulkarni S, Gao J, et al.* Severe metabolic alkalosis-a diagnostic dilemma. Respir Med Case Rep. 2018; 25:177-180. doi: 10.1016/j.rmcr.2018.08.019.
13. *Mahapatra S, Lavina A, Bello A, Mehta›s J.P.* A Rare Case of Ectopic Adrenocorticotropic Hormone Syndrome Causing Severe Hypokalemia and Metabolic Alkalosis in Small Cell Lung Cancer. Am J Respir Crit Care Med. 2022; 205:A3388. doi: 10.1164/ajrccm-conference.2022.205.1_MeetingAbstracts.A3388.
14. *Franco F, Carcereny E, Guirado M, Ortega AL, López-Castro R, Rodríguez-Abreu D, et al.* Epidemiology, treatment, and survival in small cell lung cancer in Spain: Data from the Thoracic Tumor Registry. PLoS One. 2021;16(6):e0251761. doi:10.1371/journal.pone.0251761.
15. *Hine J, Schwell A, Kairys N.* An Unlikely Cause of Hypokalemia. J Emerg Med. 2017;52(5):e187-e191. doi: 10.1016/j.jemermed.2016.12.011.
16. *Richa CG, Saad KJ, Halabi GH, Gharios EM, Nasr FL, Merheb MT.* Case-series of paraneoplastic Cushing syndrome in small-cell lung cancer. Endocrinol Diabetes Metab Case Rep. 2018; 8;2018:18-0004. doi: 10.1530/EDM-18-0004.
17. *Zhang X, Meng L, Xiao Y, Chen Z.* Case report: Radiofrequency ablation combined with biopsy for Cushing's syndrome due to ectopic ACTH lesions in the lung. Front. Oncol. 2022;12:1059308. doi: 10.3389/fonc.2022.1059308.
18. *Suyama K, Naito Y, Yoh K, Niho S, Goto K, Ohmatsu H, et al.* Development of Cushing's syndrome during effective chemotherapy for small cell lung cancer. Intern Med. 2011;50(4):335-8. doi: 10.2169/internalmedicine.50.4127.
19. *Braun J, Grinshpun A, Atlan K, Sachar S, Knigen A, Yosha-Orpaz L, et al.* Intractable Hypokalemia: a Red Herring for Rapidly Evolving Ectopic Cushing's Syndrome. Isr Med Assoc J. 2019; 21(1):60-62.
20. *Lobo Ferreira T, Nunes da Silva T, Canário D, Francisca Delerue M.* Hypertension and severe hypokalaemia associated with ectopic ACTH production. BMJ Case Rep. 2018;16;2018:bcr2017223406. doi: 10.1136/bcr-2017-223406.
21. *Mohib O, Papleux E, Remmelink M, Gottignies P, De Bels D.* An ectopic Cushing's syndrome as a cause of severe refractory hypokalemia in the ICU. Acta Clinica Belgica. 2021; 76:5, 373-378, doi: 10.1080/17843286.2020.1734162.
22. *Alba EL, Japp EA, Fernandez-Ranvier G, Badani K, Wilck E, Ghesani M, et al.* The Mount Sinai Clinical Pathway for the Diagnosis and Management of Hypercortisolism due to Ectopic ACTH Syndrome. J Endocr Soc. 2022; 6(7):bvac073. doi: 10.1210/jendso/bvac073.
23. *Raj R, Taylor RK, Owen D.* A Rapidly Progressive Case of Ectopic Adrenocorticotropic Hormone (ACTH) Syndrome. Am J Case Rep. 2021;22:e934437. doi: 10.12659/AJCR.934437.
24. *Raff H, Sharma ST, Nieman LK.* Physiological basis for the etiology, diagnosis, and treatment of adrenal disorders: Cushing's syndrome, adrenal insufficiency, and congenital adrenal hyperplasia. Compr Physiol. 2014;4(2):739-769. doi:10.1002/cphy.c130035.
25. *Lacroix A, Feelders RA, Stratakis CA, et al.* Cushing's syndrome. Lancet. 2015;386:913-927. doi: 10.1016/S0140-6736(14)61375-1.