Caspian Journal of Internal Medicine 2026 (Summer); 17(3): 681-687
DOI: 10.22088/cjim.17.3.681

Case Report

First case report of ectopic Cushing's syndrome secondary to synchronous mediastinal neuroendocrine tumors

Edita Guadalupe Ruiz-Huaranga (MD) [1, 2]
Maria del Pilar Quinones Avila (MD) [3]
Rosa Laurie Marcilla Truyenque (MD) [1]
Marcio Jose Concepcion-Zavaleta (MSc) [4*]
Jose Paz-Ibarra (PhD) [1, 5]
Jenyfer Fuentes-Mendoza [4]
Juan Eduardo Quiroz-Aldave (MD) [6]

1. Division of Endocrinology, Hospital Nacional Edgardo Rebagliati Martins, Lima, Peru
2. Universidad Peruana Cayetano Heredia, Lima, Peru
3. Division of Anatomic Pathology, Hospital Nacional Edgardo Rebagliati Martins, Lima, Peru
4. Grupo de Investigacion en Neurociencias, Metabolismo, Efectividad Clinicay Salud Publica, Universidad Científica del Sur, Lima, Peru
5. School of Medicine, Universidad Nacional Mayor de San Marcos, Lima, Peru
6. Division of Research, Hospital de Apoyo Chepen, Chepen, Peru

*** Correspondence:**
Marcio Jose Concepcion-Zavaleta, Abraham Lincoln Avenue 315, Pueblo Libre, Lima, Peru

E-mail:
marcio_conc_zav@outlook.es

Received: 16 July 2025
Revised: 5 Sep 2025
Accepted: 7 Sep 2025
Published: 1 Sep 2026

Abstract

Background: Ectopic Cushing's syndrome (ECS) is a rare cause of hypercortisolism resulting from non-pituitary adrenocorticotropic hormone (ACTH) secretion, most associated with neuroendocrine tumors (NETs) of pulmonary or gastrointestinal origin. Mediastinal NETs are an extremely rare source.

Case Presentation: We report the case of a 23-year-old male with no relevant medical history, presenting with progressive muscle weakness, hyperpigmentation, weight gain, and signs of severe hypercortisolism, including moon facies, ecchymosis, hypertension, hyperglycemia, and hypokalemia. Hormonal tests confirmed ECS with markedly elevated ACTH and cortisol levels. Imaging revealed two anterior mediastinal masses. Histopathological analysis of the surgical specimens confirmed ACTH-producing atypical NETs.

Conclusions: This case highlights the importance of considering ectopic ACTH secretion from mediastinal neuroendocrine tumors in the differential diagnosis of severe, rapidly progressive hypercortisolism. Early recognition and timely surgical management can prevent life-threatening complications and improve patient outcomes, even in rare and aggressive presentations.

Keywords: Ectopic ACTH syndrome, Cushing syndrome, Neuroendocrine tumors, Mediastinal neoplasms, Case reports

Citation:
Ruiz-Huaranga EG, Quinones Avila Mdp, Marcilla Truyenque RL, et al. First case report of ectopic Cushing's syndrome secondary to synchronous mediastinal neuroendocrine tumors. Caspian J Intern Med 2026, 17(3): 681-687.

Neuroendocrine tumors (NETs) are neoplasms originating from neuroendocrine cells and can arise in various organs, most frequently in the gastroentero pancreatic system and lungs (1). These tumors may be asymptomatic (2) or may secrete hormones such as adrenocorticotropic hormone (ACTH), leading to signs and symptoms of hypercortisolism (1).

Ectopic Cushing's syndrome (ECS), also known as paraneoplastic Cushing's syndrome, is a rare condition resulting from extrapituitary ACTH secretion. It accounts for approximately 10–20% of cases and is typically associated with more severe clinical manifestations of hypercortisolism (3-5). ECS most commonly originates from pulmonary neuroendocrine tumors (NETs), particularly small cell lung carcinoma, while pancreatic and thymic NETs are much less frequent sources (3, 4, 6, 7). The latter represent only 2–4% of anterior mediastinal tumors (8) and approximately 5% of thymic tumors (9, 10).

A literature search conducted in the Scopus, Web of Science, and PubMed databases revealed no previously reported cases of synchronous ACTH-producing mediastinal NETs. The estimated incidence of these tumors is 0.02–0.04 per 100,000 individuals per year, with a slight male predominance and peak incidence in the third to fourth decades of life (4, 11, 12).

The clinical presentation of ECS varies depending on tumor characteristics, patient age, and the severity and duration of cortisol excess (9, 13, 14). While some cases may mimic classic Cushing's disease, ECS often presents with rapid-onset, severe hypercortisolism and catabolic features such as muscle wasting and weight loss, rather than centripetal obesity (4, 5, 7, 13). Marked hyperpigmentation is uncommon (< 20%) and is typically associated with elevated levels of proopiomelanocortin-derived peptides (3, 12, 15).

Severe hypokalemia (<3.65 mmol/L) is a frequent finding (13, 14, 16), and correlates with disease severity, as does elevated lactate dehydrogenase (>1.3 × ULN). In addition, elevated urinary free cortisol levels (>10.5 × ULN) have been associated with improved diagnostic accuracy for ECS (17). Once ACTH-dependent Cushing's syndrome is diagnosed, differentiating Cushing's disease (pituitary origin) from ectopic ACTH secretion requires a combination of biochemical and imaging tests (4, 18, 19). Dynamic tests such as the high-dose dexamethasone suppression test (HDDST), corticotropin-releasing hormone (CRH) and/or desmopressin stimulation tests, and inferior petrosal sinus sampling (IPSS) can be useful19. Most pituitary corticotroph adenomas retain glucocorticoid receptors, allowing suppression of ACTH secretion under HDDST, and often overexpress CRH and vasopressin (V2 and V1b) receptors. In contrast, ectopic tumors typically lack these features and therefore fail to suppress. However, this distinction is not absolute; false positives and negatives can occur, particularly in well-differentiated NETs and in some atypical pituitary adenomas lacking the expected receptor expression (7).

Contrast-enhanced CT of the neck, chest, abdomen, and pelvis remains the initial imaging modality of choice12. Localization can be challenging in cases of occult or small-volume tumors, particularly bronchial NETs. In such scenarios, functional imaging especially PET/CT with somatostatin receptor ligands labeled with Gallium-68 has shown tumor detection rates of up to 80%5.

NETs are classified into histological grades from G1 (well differentiated) to G3 (poorly differentiated), based on mitotic count and the Ki-67 cell proliferation index. This classification is critical for determining prognosis and selecting the appropriate therapeutic strategy (9, 20).

Therapeutic options for ECS depend on the underlying tumor13. Surgical resection is the treatment of choice and can be curative (5, 9). In unresectable or metastatic disease, medical therapy (e.g., ketoconazole, metyrapone, mitotane), radiotherapy, chemotherapy, and targeted therapies may be required (9, 14). However, thymic or mediastinal NETs typically exhibit more aggressive clinical behavior and worse prognosis compared to other NETs of similar stage and grade (11, 19). In this report, we present the case of a male patient who developed severe hypercortisolism due to ectopic ACTH secretion from two synchronous mediastinal neuroendocrine tumors.

The clinical relevance of this report lies in raising awareness of synchronous ACTH-producing mediastinal neuroendocrine tumors as an exceptional but important cause of ectopic Cushing's syndrome. Their presentation may mimic more common conditions such as pituitary Cushing's disease, primary adrenal disorders, or other secondary causes of hypertension and metabolic derangements. Recognizing this rare entity is crucial, as should be considered in the differential diagnosis of patients with severe, refractory hypertension, hypokalemia, and rapidly progressive features of hypercortisolism.

This case report was conducted in accordance with ethical standards for clinical research. It received approval from the Institutional Research Ethics Committee of the Faculty of Medicine, Universidad Nacional de Trujillo, in accordance with national regulations and the Declaration of Helsinki. The approval code is of. N° 89-2025-UNT-FM-C.E. Informed consent was obtained from the patient for publication of this case and accompanying images. Confidentiality and anonymity were guaranteed throughout the process.

Case Presentation

A 23-year-old male patient with no relevant medical or family history presented with a 14-month history of insidious onset and progressive symptoms, including proximal muscle weakness, hyperpigmentation of the skin and nails, and a 25-kg weight gain. Physical examination revealed elevated blood pressure (170/110 mmHg), body weight of 70 kg, and height of 1.70 m. There was generalized hyperpigmentation of the skin, nails, and mucous membranes; moon facies; a dorsocervical hump; and supraclavicular fat pads. Additional findings included acne, atrophic skin, and marked ecchymoses at venipuncture sites. Purplish-red striae, greater than 2 cm in width, were observed on the abdomen, arms, and proximal regions of both legs. Muscle hypotrophy and weakness were evident, predominantly in the proximal muscles, along with bilateral lower limb edema (figure 1).

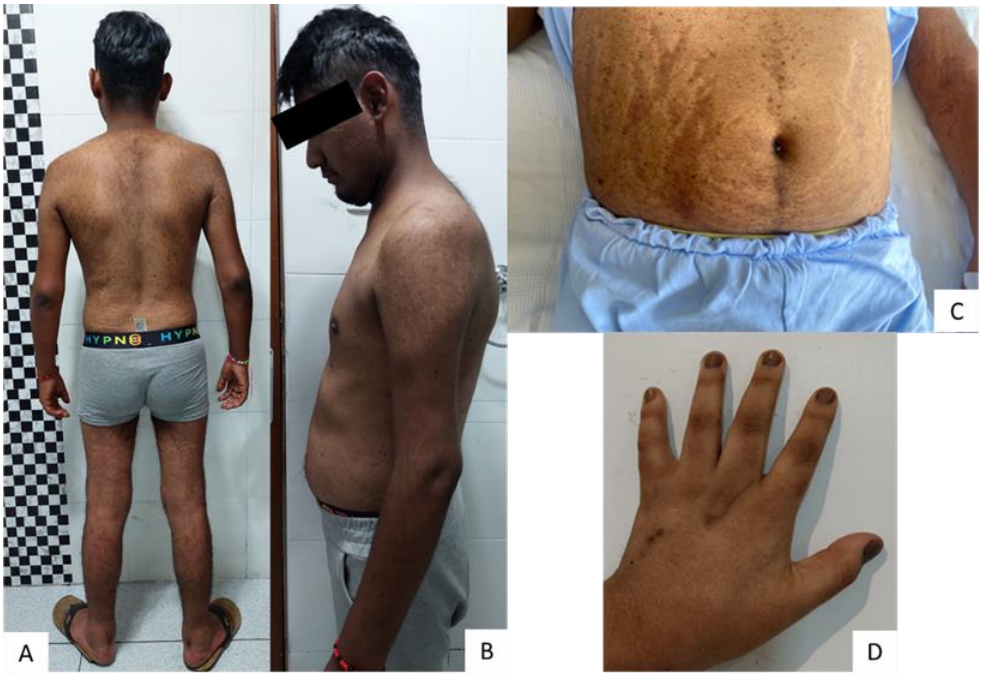

Figure 1. Clinical characteristics of the patient at the time of diagnosis. A) Muscle hypotrophy with evidence of distal edema in both lower limbs. Broad striae may be evident in the proximal region of both lower limbs. B) Generalized hyperpigmentation of the skin, dorsocervical hump, and acne lesions. C) Chronic-appearing striae greater than 2 cm wide located on the abdomen. D) Hyperpigmentation of the nails and bruising at venipuncture sites.

Laboratory tests revealed persistent severe hypokalemia (1.97 mmol/L), hypernatremia (146 mmol/L), elevated lactate dehydrogenase (LDH: 457 U/L; reference range: 140–280 U/L), hypophosphatemia (2.1 mg/dL), and fasting hyperglycemia (130 mg/dL). Cardiac enzymes were within normal limits, and the electrocardiogram showed no abnormalities. Given the clinical features suggestive of hypercortisolism, urinary free cortisol (UFC) was markedly elevated, exceeding 20 times the upper limit of normal. Dynamic testing with 2 mg (Low-Dose Dexamethasone Suppression Test, LDDST) and 8 mg (High-Dose Dexamethasone Suppression Test, HDDST) dexamethasone revealed no cortisol suppression. Plasma ACTH levels were markedly elevated, exceeding the laboratory detection limit (>1250 pg/mL) (table 1).

Table 1. Hormonal tests performed on the patient before and after surgery

	Prior to surgery	Dexamethasone suppression test	First postoperative day
Basal cortisol (Normal: 5–25 µg/dL)	28	LDDST: 23.5 HDDST: 25.7	<1
ACTH (Normal: 10–48 pg/mL)	> 1250	-	5.66
UFC (Normal: 6–75 µg/24 h)	Sample 1: 1416 Sample 2: 2884	-	-

ACTH: adrenocorticotropic hormone; HDDST: High-Dose Dexamethasone Suppression Test; LDDST: Low-Dose Dexamethasone Suppression Test; UFC: 24-hour urine free cortisol.

Review of contrast-enhanced CT images revealed two anterior mediastinal masses located on the right parasagittal plane. The superior mass, situated between the superior vena cava and the origin of the brachiocephalic trunk, measured 47 × 47 × 37 mm. The second, larger and rounded mass was located inferior to the first, with no evidence of continuity between them, and measured 91 × 92 × 96 mm (figure 2). A biopsy of the larger mass confirmed a diagnosis of a G2 ACTH-producing mediastinal neuroendocrine tumor. Bone densitometry demonstrated severe osteopenia in the lumbar spine, and transthoracic echocardiography showed no pericardial involvement.

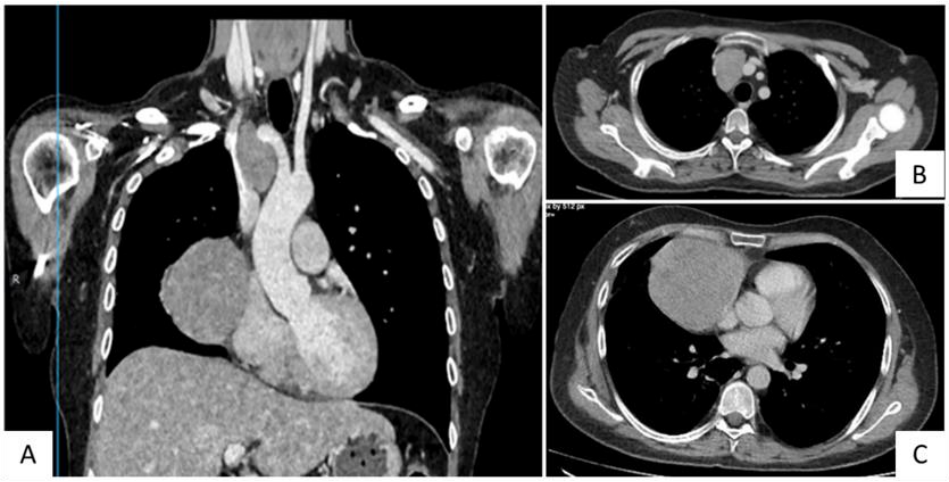

Figure 2. Coronal and transverse sections of a contrast-enhanced chest CT scan. A) Coronal section showing both anterior mediastinal masses, located on the right parasagittal plane; no connection between them is evident. B) Transverse section, first mass, measuring 47x47x37 mm. C) Transverse section, second mass, measuring 91x92x96 mm.

With a diagnosis of ectopic Cushing's syndrome secondary to synchronous mediastinal neuroendocrine tumors, the patient received initial medical therapy with ketoconazole 200 mg TID, a steroidogenesis inhibitor; three antihypertensive agents, including spironolactone 50 mg QD, to manage hypertension and hypokalemia; enoxaparin 40 mg subcutaneously every 24 hours for thromboprophylaxis; and cotrimoxazole 160/800 mg QD for Pneumocystis jirovecii prophylaxis. The patient subsequently underwent median sternotomy with resection of both tumors, measuring approximately 10 × 11 cm and 5 × 8 cm. The smaller tumor infiltrated the thymus and had compromised margins. Histopathological examination confirmed both tumors as mediastinal neuroendocrine tumors. Immunohistochemistry was positive for pancytokeratin, chromogranin, synaptophysin, CD56, and granular cytoplasmic ACTH. The Ki-67 index was <1%, and the mitotic count was 5 per 10 high-power fields, with foci of necrosis and hemorrhage, consistent with intermediate-grade (G2) atypical NETs (figure 3).

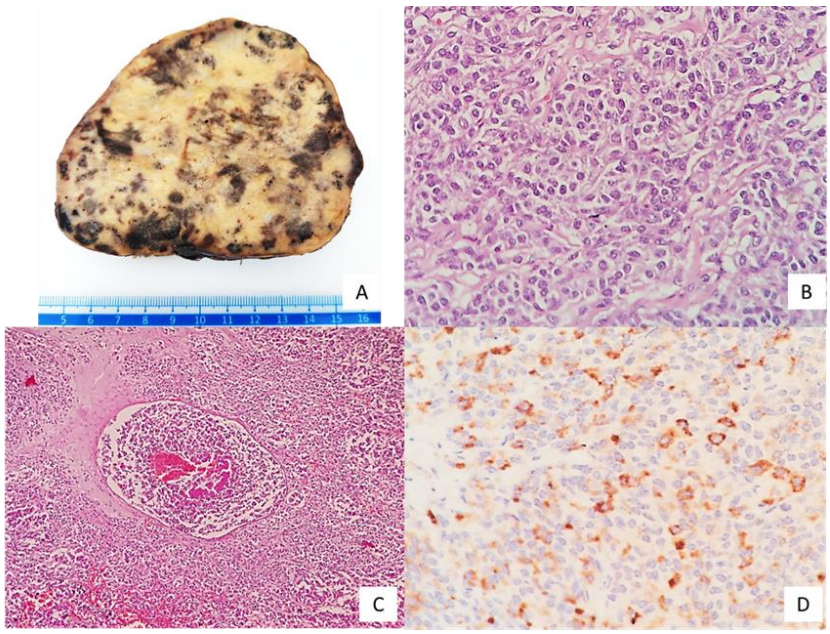

Figure 3. Histopathological study of the surgical specimen. **A) Larger tumor, partially delimited by a thin capsule; yellowish cut surface with areas of hemorrhage. B) Proliferation of cuboidal cells arranged in an organoid pattern, with nuclear atypia and some mitoses observed (HE – 400X). C) Presence of necrosis (HE – 100X). D) Positive immunohistochemistry for ACTH (400X).**

The patient developed transient central adrenal insufficiency secondary to the resolution of hypercortisolism and was started on prednisone 10 mg daily as replacement therapy (table 1). Blood pressure and serum electrolyte levels normalized, and clinical improvements were noted, including reduced muscle weakness and decreased hyperpigmentation (figure 4). Follow-up CT imaging showed postsurgical changes without residual masses in the mediastinum or lungs. An 18FDG PET-CT scan revealed no hypermetabolic activity. Adjuvant treatment included external beam radiotherapy. One year after treatment, the patient remains free of tumor recurrence and biochemical abnormalities under regular follow-up with the Endocrinology Department.

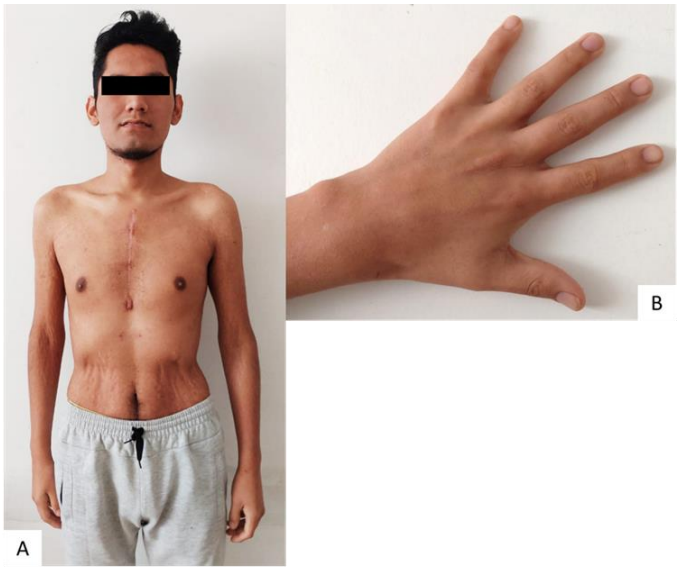

Figure 4. Patient clinical characteristics at one year of follow-up. **A) Skin depigmentation, weight recovery, and reduction in edema. B) Nail depigmentation and decreased edema.**

Discussion

In this case, we present a patient who developed Cushing's syndrome (CS) due to ectopic ACTH secretion from two synchronous mediastinal NETs, one of which infiltrated the thymus. Notably, ECS caused by mediastinal or thymic carcinoids remains a rare and serious condition. Thymic carcinoids associated with CS generally have a worse prognosis than those without CS, although it remains unclear whether this is due to their intrinsic biological behavior or the systemic complications of hypercortisolism (7, 9, 12). Regarding clinical presentation, our patient presented violaceous striae wider than 1 cm, hyperpigmentation, proximal muscle weakness, and spontaneous bruising. He also exhibited complications related to severe hypercortisolism, including hyperglycemia, severe hypokalemia, lymphopenia, osteoporosis, and refractory hypertension.

In patients with severe clinical, metabolic, and biochemical disturbances such as in our case rapid control of hypercortisolism is essential once the tumor is localized3. The diagnostic strategy should include a prompt and systematic assessment of comorbidities, with early initiation of both preventive and therapeutic interventions to optimize outcomes (7, 10). In patients with ectopic Cushing's syndrome (CS), as in our case, the diagnosis is often straightforward due to the severity of hypercortisolism. From a practical standpoint, the primary objective is to identify the presence of an overt and potentially aggressive tumor that may require urgent surgical excision and/or antineoplastic therapy (7, 13). In cases of severe CS with multiple complications, reducing hypercortisolism should be considered an endocrinological emergency. The therapeutic decision whether surgical removal of a localized tumor, medical therapy, or bilateral adrenalectomy should ideally be made by an experienced multidisciplinary team, tailored to the patient's clinical status (12, 21).

Surgical excision remains the treatment of choice and offers the potential for cure (4, 9). When successful, as in our case, it leads to prompt resolution of hypercortisolism while preserving long-term adrenal function, although transient postoperative corticotropic insufficiency may occur (5, 16). If the tumor is unresectable due to local invasion or metastatic disease, systemic chemotherapy may be indicated, and pharmacologic management of hypercortisolism becomes essential. Therapeutic options

include steroidogenesis inhibitors (ketoconazole, metyrapone, etomidate, olisodrostat), glucocorticoid receptor antagonists (mifepristone), adrenolytic agents (mitotane), and bilateral adrenalectomy (9, 14, 22).

Additional treatment modalities include radiotherapy, which may be appropriate for incompletely resected or poorly differentiated carcinoid tumors (7, 11). Systemic chemotherapy with etoposide, cisplatin, 5-fluorouracil, or doxorubicin is used for metastatic NETs and small cell carcinomas9. Somatostatin analogs (e.g., long-acting octreotide and pasireotide) have demonstrated antiproliferative effects in various case reports (3, 19). Although data are limited, targeted therapies including tyrosine kinase inhibitors, VEGFR inhibitors, and mTOR inhibitors are under consideration for thymic NETs (7, 19, 21). The role of lutetium-based peptide receptor radionuclide therapy (PRRT) in mediastinal carcinoids remains uncertain, though its success in other NET types suggests it may be a viable option when available (14).

Importantly, mediastinal/thymic NETs exhibit aggressive clinical behavior, with a high risk of local recurrence and metastasis, closely tied to the tumor's histological grade (11, 19, 21, 23). These tumors generally carry a worse prognosis than pulmonary or other NETs of comparable stage and grade (11, 16, 19). Reported median survival times are approximately 110 months for localized, 59 months for locally advanced, and 35 months for metastatic disease. Stratified by tumor grade, median survival times are 78, 43, and 23 months for low-, intermediate-, and high-grade NETs, respectively19. Therefore, close and periodic follow-up is essential for long-term management of these patients.

ECS caused by a mediastinal NET is a rare and clinically challenging condition, often associated with serious complications. Clinicians should maintain a high index of suspicion for ectopic ACTH secretion in patients with abrupt-onset, severe Cushing's syndrome especially when accompanied by hypokalemia and hypertension refractory to standard therapy. Prompt localization of the source and early multidisciplinary intervention are paramount to improving prognosis, even in aggressive and rare tumor presentations.

Acknowledgments

Not applicable.

Funding: This article did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics approval: Of. N: 89-2025-UNT-FM-C.E.

Conflict of interests: The authors declare that they have no conflicts of interest to disclose.

Authors' contribution: Edita Guadalupe Ruiz-Huaranga: Investigation, Resources, Writing - Original Draft, Writing - Review & Editing. María del Pilar Quiñones Ávila: Investigation, Writing - Original Draft, Writing - Review & Editing. Rosa Laurie Marcilla Truyenque: Investigation, Writing - Original Draft, Writing - Review & Editing. Marcio Concepción-Zavaleta: Conceptualization, Methodology, Investigation, Writing - Original Draft, Writing - Review & Editing, Supervision, Project administration. José Paz-Ibarra: Methodology, Investigation, Writing - Original Draft, Writing - Review & Editing. Jenyfer Fuentes-Mendoza: Investigation, Writing - Original Draft. Juan Eduardo Quiroz-Aldave: Investigation, Writing - Original Draft, Writing - Review & Editing.

References

1. Oronsky B, Ma PC, Morgensztern D, Carter CA. Nothing but NET: a review of neuroendocrine tumors and carcinomas. Neoplasia 2017; 19: 991-1002.
2. Kulke MH, Shah MH, Benson AB, et al. Neuroendocrine tumors, version 1.2015. J Natl Compr Canc Netw 2015; 13: 78-108.
3. Young J, Haissaguerre M, Viera-Pinto O, et al. Management of endocrine disease: Cushing's syndrome due to ectopic ACTH secretion: an expert operational opinion. Eur J Endocrinol 2020; 182: R29-58.
4. Hayes AR, Grossman AB. Distinguishing Cushing's disease from the ectopic ACTH syndrome: Needles in a haystack or hiding in plain sight? J Neuroendocrinol 2022; 34: e13137.
5. Ragnarsson O, Juhlin CC, Torpy DJ, Falhammar H. A clinical perspective on ectopic Cushing's syndrome. Trends Endocrinol Metab 2024; 35: 347-360.
6. Miao H, Lu L, Zhu H, et al. Experience of ectopic adrenocorticotropin syndrome: 88 cases with identified causes. Endocr Pract 2021; 27: 866-73.
7. Jia R, Sulentic P, Xu JM, Grossman AB. Thymic neuroendocrine neoplasms: biological behavior and therapy. Neuroendocrinology 2017; 105: 105-14.
8. Abelian K, Akano OI, Penha D, Guedes-Pinto E, Ntouskou M. Carcinoid tumor of the anterior mediastinum in a 38-year-old woman. Radiol Case Rep 2020; 15: 2018-21.
9. Pan J, Lin W, Zong L, et al. Ectopic ACTH syndrome caused by thymic neuroendocrine tumor: a case report and literature review. Ann Palliat Med 2022; 11: 1575-81.

10. Landry I, Medina Mora LA, Siddiqui R, Tumarinson T, Reich DM. Atypical carcinoid tumor of the mediastinum presenting as Cushing's syndrome in an otherwise healthy young male. Cureus 2021;13: e14940.
11. Gunay YE, Nuhoglu I, Kisioglu SV, Ersoz S, Tufekci D. Ectopic Cushing's syndrome due to thymic neuroendocrine tumor treated with surgery and radiotherapy. J Coll Physicians Surg Pak 2022; 32: 944-7.
12. Ramirez-Renteria C. Ectopic hormonal syndromes: Cushing's syndrome and acromegaly. Arch Med Res 2023; 54: 102898.
13. Zhou Z, Chai W, Yang L, et al. Successful resolution of ectopic Cushing syndrome by minimally invasive thoracoscopic resection of the neuroendocrine tumor of the thymus: a rare case report. BMC Surg 2022; 22: 226. doi:10.1186/s12893-022-01674-0.
14. Valassi E. Clinical presentation and etiology of Cushing's syndrome: Data from ERCUSYN. J Neuroendocrinol 2022; 34: e13114.
15. Shekhar S, Dharmshaktu P. On the palms of his hands: ACTH-induced hyperpigmentation. Am J Med 2018; 131: 144-5.
16. Bohnenberger H, Dinter H, König A, Ströbel P. Neuroendocrine tumors of the thymus and mediastinum. J Thorac Dis 2017; 9: S1448-57.
17. Furnica R, Collard A, Cornelis F, Alexopoulou O, Maiter D. Urinary free cortisol is an independent predictive factor for early distinction between ectopic ACTH secretion and pituitary Cushing's disease. Endocrine Abstracts 2023; 90: P391.
18. Ferriere A, Tabarin A. Biochemical testing to differentiate Cushing's disease from ectopic ACTH syndrome. Pituitary 2022; 25: 705-8.
19. Qiu Y, Zhao H, Pan H, et al. Localization diagnosis of adrenocorticotrophic hormone-dependent Cushing's syndrome: two case reports and literature review. Ann Palliat Med 2022; 11: 3804-17.
20. Zhang JY, Kunz PL. Making sense of a complex disease: a practical approach to managing neuroendocrine tumors. JCO Oncol Pract 2022; 18: 258-64.
21. Ershadi R, Vahedi M, Jahanbin B, Sarbazzadeh J, Rafieian S. Cushing syndrome secondary to a mediastinal carcinoid tumor: a case report. Int Cancer Conf J 2022; 11: 152-7.
22. Marques JVO, Boguszewski CL. Medical therapy in severe hypercortisolism. Best Pract Res Clin Endocrinol Metab 2021; 35: 101487.
23. Li LY, Zhao HY, Tong HC, et al. Atypical thymic carcinoid tumor with ectopic ACTH syndrome in a 33-year-old male patient: A rare case report and literature review. Medicine (Baltimore) 2023; 102: e33847.