



Thymoma Masquerading as Cushing Syndrome: A Rare Case of Ectopic ACTH Secretion from Atypical Thymic Carcinoid (Grade 2 NEC)

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Abstract

Background: Ectopic adrenocorticotrophic hormone (ACTH) secretion (EAS) accounts for 9%–18% of ACTH-dependent Cushing's syndrome (CS) cases. Thymic neuroendocrine tumours (NETs), comprising only 2%–5% of all thymic neoplasms, represent a rare but clinically significant cause of EAS. We present an unusual case where an atypical thymic carcinoid (Grade 2 neuroendocrine carcinoma) presented as florid Cushing syndrome, complicated by opportunistic infection and severe end-organ manifestations.

Case Presentation: A 54-year-old male presented with an 18-month history of bilateral facial puffiness, progressive proximal muscle weakness, hyperpigmentation of the lower limbs, and right-sided visual loss. Biochemical evaluation confirmed severe ACTH-dependent hypercortisolism with non-suppressible cortisol, markedly elevated plasma ACTH ($>3 \times$ upper limit of normal), and hypokalemic metabolic alkalosis. Imaging revealed a 5.2×4.0 cm heterogeneously enhancing anterior mediastinal mass. Ga-68 DOTATATE PET-CT demonstrated intense tracer avidity (SUVmax 14.6), confirming somatostatin receptor expression. The patient underwent successful R0 thymectomy via median sternotomy. Histopathology confirmed an atypical thymic carcinoid (Grade 2 NEC) with ACTH, synaptophysin, and chromogranin A positivity.

Conclusion: This case highlights the diagnostic challenge of ectopic ACTH-secreting thymic NETs, which can mimic pituitary-dependent Cushing disease. A high index of clinical suspicion, systematic biochemical workup, and functional imaging (Ga-68 DOTATATE PET-CT) are essential. Complete R0 surgical resection remains the cornerstone of curative management.

Keywords: Ectopic ACTH syndrome; Thymic neuroendocrine tumour; Cushing syndrome; Thymoma; Paraneoplastic; Atypical carcinoid; Grade 2 NEC; Ga-68 DOTATATE PET-CT; Median sternotomy; R0 resection.

1. Introduction

Cushing's syndrome (CS) secondary to ectopic ACTH secretion (EAS) is a diagnostically challenging clinical entity, necessitating a systematic and multidisciplinary approach for accurate localisation of the responsible neoplasm. EAS accounts for approximately 9%–18% of all ACTH-dependent CS cases¹. While bronchial carcinoids and small-cell lung carcinomas constitute the most frequently identified aetiologies, thymic neuroendocrine tumours represent a distinctly rare subset, responsible for only 5%–10% of EAS cases^{2,3}.

Thymic NETs arise from neuroendocrine cells within the thymic epithelium and encompass a biological spectrum from well-differentiated typical carcinoids to aggressive atypical carcinoids and large/small-cell neuroendocrine carcinomas, as classified by the WHO 2021 classification of thoracic tumours¹¹. Their association with EAS confers a particularly aggressive clinical course, frequently presenting with severe hypercortisolism, opportunistic infections, and marked catabolism. The diagnosis is often delayed because the clinical picture closely overlaps with pituitary-dependent CS (Cushing disease), and the mediastinal origin may be overlooked without dedicated functional imaging⁶.

Ga-68 DOTATATE PET-CT has emerged as the gold-standard functional imaging modality for somatostatin receptor (SSTR)-expressing neoplasms, with superior sensitivity compared to conventional octreotide scintigraphy¹⁰. This capability is particularly valuable in thymic NETs, which often express SSTR2 and SSTR5 subtypes.

Here we present a diagnostically instructive case of a 54-year-old man whose 18-month history of cushingoid features, progressive

myopathy, and visual loss ultimately led to the discovery of an atypical thymic carcinoid (Grade 2 NEC) with intense somatostatin receptor expression. This case adds to the limited published literature on thymic NET-associated EAS and underscores the importance of functional imaging and timely surgical intervention.

2. Case Presentation

2.1 Clinical History

A 54-year-old male was referred to the Endocrinology Department with an 18-month history of bilateral facial puffiness. On directed inquiry, he described progressive inability to rise from a seated position consistent with proximal myopathy, significant darkening of skin patches over both lower limbs (hyperpigmentation), and recent onset of right-sided visual loss. There was no history of exogenous corticosteroid use, and no family history of multiple endocrine neoplasia (MEN1) syndrome.

On clinical examination, there was marked loss of muscle bulk consistent with proximal myopathy and mild truncal obesity. His body mass index was 20 kg/m², suggesting significant lean mass depletion secondary to hypercortisolism-induced catabolism. Ophthalmological evaluation revealed choroiditis with exudative retinal detachment in the right eye a recognised complication of severe hypercortisolism-associated opportunistic infection, most commonly *Pneumocystis jirovecii*.

2.2 Biochemical Workup

Biochemical evaluation demonstrated the hallmarks of severe ACTH-dependent hypercortisolism, as summarised in Table 1. There was complete loss of diurnal cortisol variation, urinary free cortisol more than three times the upper limit of normal, markedly elevated plasma ACTH ($>3\times$ ULN), and non-suppressibility on both

overnight low-dose dexamethasone suppression test (ONDST, 1 mg) and high-dose dexamethasone suppression test (HDDST, 8 mg). The absence of suppression on HDDST strongly pointed towards an ectopic rather than a pituitary

source of ACTH¹⁴. Concomitant severe hypokalaemia with metabolic alkalosis classical features of ectopic ACTH syndrome due to mineralocorticoid receptor activation by excess cortisol were documented.

Table 1: Biochemical profile at presentation

Investigation	Value	Reference Range	Significance
Serum Cortisol (8 AM)	Elevated (non-suppressible)	5–25 µg/dL	↑↑ Hypercortisolism
Plasma ACTH	>3× ULN	< 46 pg/mL	ACTH-dependent CS
24h Urinary Free Cortisol	>3× ULN	< 50 µg/24h	Overt hypercortisolism
Overnight 1 mg DST	Non-suppressible	Suppression < 1.8 µg/dL	Autonomous cortisol secretion
High-Dose DST (8 mg)	Non-suppressible	> 50% suppression expected	Ectopic ACTH source
Serum Potassium	Severe hypokalemia	3.5–5.0 mEq/L	Mineralocorticoid excess
Blood Gas	Metabolic alkalosis	pH 7.35–7.45	Hypokalemic alkalosis
Diurnal Cortisol Variation	Lost	PM < 50% AM	HPA axis dysregulation

ACTH = adrenocorticotrophic hormone; DST = dexamethasone suppression test; ONDST = overnight dexamethasone suppression test; HDDST = high-dose dexamethasone suppression test; ULN = upper limit of normal; CS = Cushing syndrome; HPA = hypothalamic-pituitary-adrenal.

2.3 Radiological Investigations

Contrast-enhanced computed tomography (CECT) of the thorax demonstrated a moderately enhancing, well-defined solid anterior mediastinal mass measuring 3.8 × 4.5 × 5.0 cm, with an additional contiguous lobule measuring 4.8 × 1.5 × 3.7 cm arising

from the left lobe of the thymus. Fat planes were preserved with no evidence of local vascular or pleural invasion (Figure 1). The radiological features were initially interpreted as potentially consistent with thymoma.

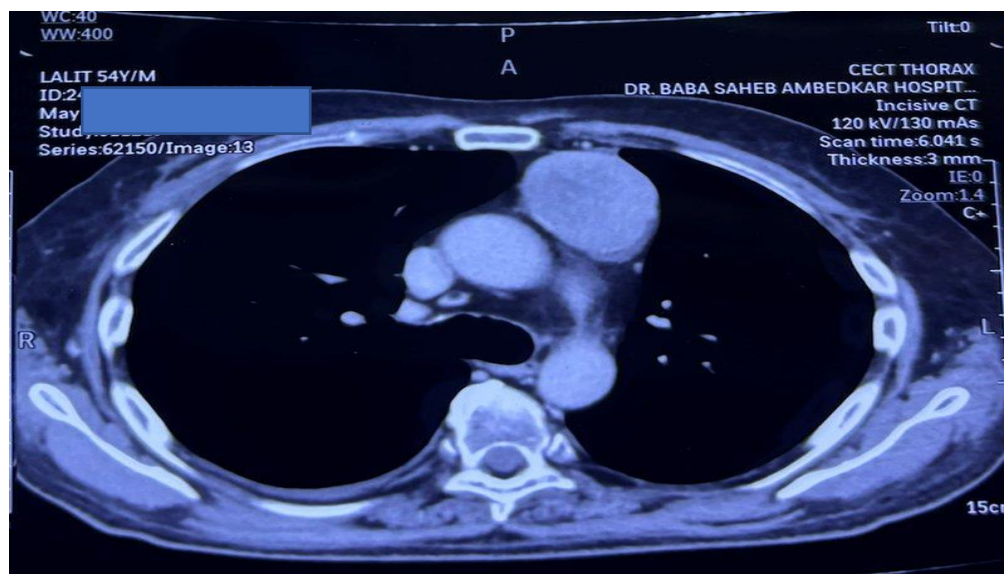


Figure 1: CECT Thorax (axial view): Heterogeneously enhancing anterior mediastinal mass (5.2 × 4.0 cm) in the left paramedian region with intact fat planes and no evidence of local invasion.

Ga-68 DOTATATE PET-CT revealed intense tracer uptake (SUVmax 14.6) within the anterior mediastinal lesion (Figure 2), confirming robust somatostatin receptor expression a characteristic feature of well- to moderately-differentiated neuroendocrine neoplasms¹⁰. This high SUVmax value effectively reclassified the

lesion from a presumed thymoma to a somatostatin receptor-positive thymic NET, directly guiding further management. Importantly, physiological uptake was noted in the adrenal glands bilaterally, reflecting adrenal hyperplasia secondary to chronic ACTH stimulation a corroborating functional finding.

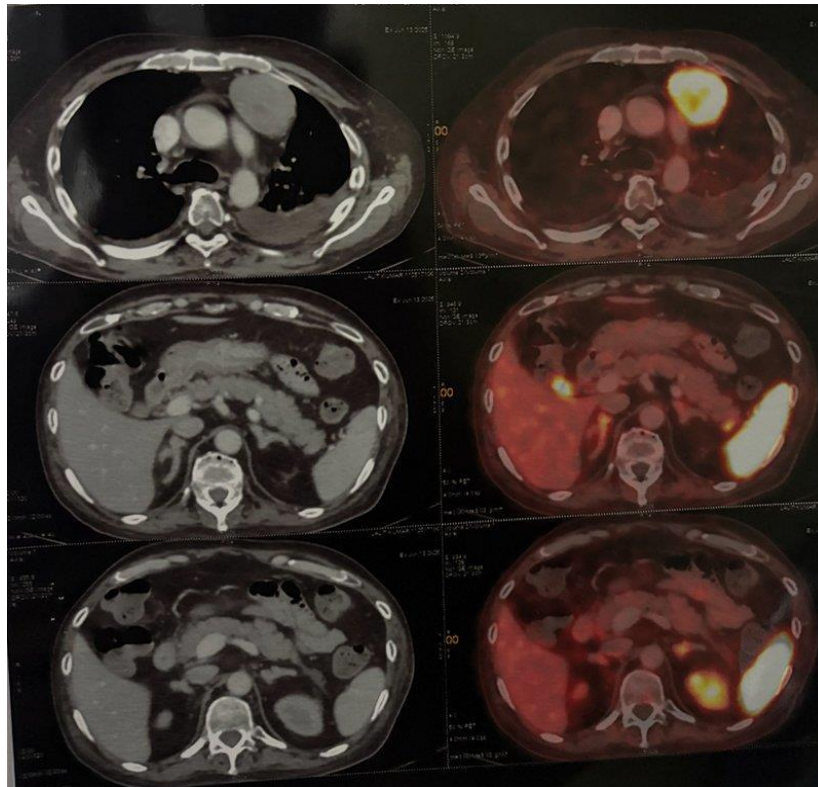


Figure 2: Ga-68 DOTATATE PET-CT (coronal and axial fusion images): Intense tracer uptake in the anterior mediastinal mass (SUVmax 14.6), confirming somatostatin receptor expression. Bilateral adrenal hyperplasia is visualised on the CT component, consistent with chronic ACTH stimulation.

2.4 Surgical Management

Following multidisciplinary team (MDT) discussion involving cardiothoracic surgery, endocrinology, and nuclear medicine, and after optimisation of the patient's metabolic status with correction of hypokalaemia (potassium supplementation and spironolactone), empirical antifungal therapy (voriconazole) for the suspected ocular opportunistic infection, and pre-operative cortisol management with ketoconazole, the patient underwent elective thymectomy via median sternotomy under general anaesthesia.

Intraoperative findings confirmed a bilobed anterior mediastinal mass originating from the left thymic lobe, with entirely intact fat planes and no evidence of pleural or pericardial involvement. A complete R0 resection was achieved with extended mediastinal lymphadenectomy. The gross surgical specimen demonstrated a bilobed mass measuring approximately 5×4 cm with areas of haemorrhage and focal necrosis (Figure 3). The post-operative course was uncomplicated.

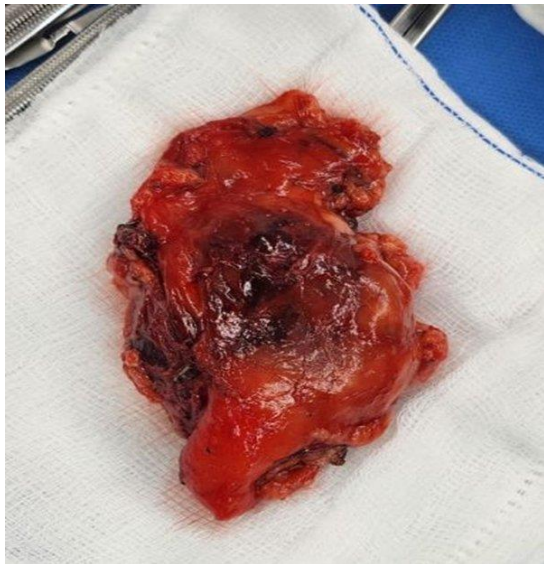


Figure 3: Gross surgical specimen following R0 thymectomy: Bilobed anterior mediastinal mass (approximately 5 × 4 cm) with areas of haemorrhage and necrosis consistent with a neuroendocrine neoplasm.

2.5 Histopathological and Immunohistochemical Findings

Microscopic examination of haematoxylin and eosin (H&E) stained sections revealed sheets and nests of tumour cells with moderate cytoplasm, vesicular nuclei, and prominent nucleoli (Figure 4a). Mitotic activity was brisk with focal areas of comedo-type necrosis.

Immunohistochemistry demonstrated diffuse strong nuclear positivity for Ki-67 (>20%), consistent with Grade 2 neuroendocrine carcinoma according to the WHO 2021 classification of thoracic tumours¹¹ (Figure 4b). Additional immunostains confirmed positivity for ACTH (confirming ectopic hormone production), synaptophysin, and chromogranin A — a panel diagnostic of neuroendocrine differentiation. The complete morphological and immunophenotypic profile was consistent with an Atypical Thymic Carcinoid (Grade 2 NEC). All resection margins were negative (R0).

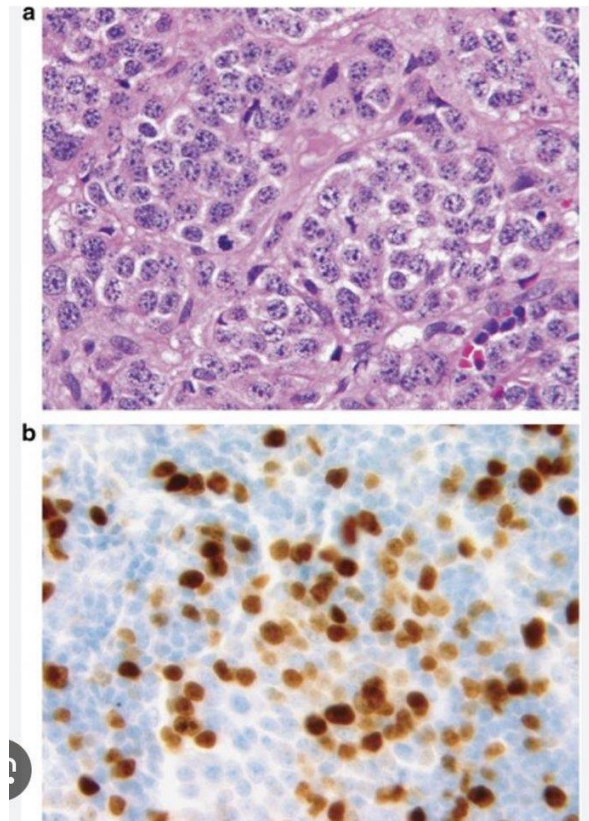


Figure 4: Histopathological findings. (a) H&E stain (×200): Sheets of neoplastic cells with moderate cytoplasm, vesicular nuclei, and brisk mitotic activity with focal necrosis. (b) Ki-67 immunohistochemistry: Diffuse strong nuclear positivity (>20%), confirming Grade 2 neuroendocrine carcinoma per WHO 2021.

3. Discussion

This case illustrates the rare but diagnostically challenging presentation of an ACTH-secreting thymic NET. Thymic NETs account for only 2%–5% of all thymic neoplasms², yet constitute the second most common cause of EAS after bronchial carcinoids in certain series, with an estimated incidence of 5%–10% within the EAS category^{1,3}. Unlike more common thymomas, thymic NETs are biologically aggressive, with a significantly higher recurrence rate and tendency for locoregional invasion and distant metastases.

While EAS classically presents with rapid-onset, florid Cushing syndrome, the chronicity of our patient's symptoms (18 months) underscores the variable pace of disease progression and the substantial risk of diagnostic delay, as previously documented by Neary et al. in their 25-year single-centre experience³. This delay carries significant clinical consequences: protracted hypercortisolism leads to immunosuppression, opportunistic infection, progressive catabolism, and potentially irreversible end-organ damage as exemplified by our patient's choroidal involvement.

The ophthalmological complication choroiditis with exudative retinal detachment merits particular emphasis. Severe endogenous hypercortisolism is an independent risk factor for opportunistic infections including *Pneumocystis jirovecii* choroiditis. Clinicians must maintain a high index of suspicion for such complications, particularly when patients present with visual symptoms in the context of CS, as these may represent the initial presentation of severe immunosuppression. Empirical antifungal or antipneumocystis treatment should be initiated early, as untreated choroidal infection may lead to permanent visual loss.

The differential diagnosis of ACTH-dependent CS is a two-step process: first, confirming autonomous ACTH-dependent hypercortisolism biochemically; second, distinguishing pituitary-dependent Cushing disease (CD) from ectopic ACTH syndrome (EAS). The pattern observed in our patient severely elevated ACTH, markedly raised 24-hour urinary free cortisol ($>3\times$ ULN), complete loss of diurnal variation, and non-suppressibility on HDDST is characteristic of ectopic rather than pituitary-dependent CS, as per

Endocrine Society guidelines¹⁴ and the expert operational opinion of Young et al.¹. Ga-68 DOTATATE PET-CT has emerged as the gold-standard functional imaging modality for localising SSTR-expressing neuroendocrine neoplasms^{10,15}. The intense tracer uptake in our case (SUVmax 14.6) facilitated definitive lesion characterisation and excluded distant metastases, directly informing the surgical decision. Notably, bilateral adrenal hyperplasia on PET-CT served as additional corroborating evidence of chronic ectopic ACTH stimulation. This case reinforces the recommendation that Ga-68 DOTATATE PET-CT should be performed in all patients with confirmed EAS when the ectopic source has not been localised by conventional CT/MRI alone.

Complete surgical resection (R0 thymectomy) represents the only potentially curative treatment for thymic NETs^{5,12}. The completeness of resection is the strongest independent prognostic determinant for overall survival and recurrence-free survival^{5,6}. Per available literature and ESMO guidelines¹⁵, no benefit from adjuvant therapy has been demonstrated for completely resected thymic carcinoids. Median sternotomy with radical mediastinal lymph node dissection as employed in our patient provides optimal exposure and the best oncological platform for achieving negative resection margins. When R0 resection cannot be achieved, cytoreductive surgery, somatostatin analogues, targeted therapy with everolimus, or peptide-receptor radionuclide therapy (PRRT) may be considered in experienced multidisciplinary centres^{8,9}.

This case also highlights an important diagnostic pitfall: the initial radiological interpretation of an anterior mediastinal mass as a thymoma. Given the overlapping imaging appearances, Ga-68 DOTATATE

PET-CT should be performed early in the evaluation of any anterior mediastinal mass in a patient with biochemical evidence of EAS, as the functional characterisation fundamentally alters both the diagnosis and surgical planning^{6,10}. The high SUVmax (14.6) in our case was pivotal in establishing the neuroendocrine nature of the lesion prior to surgery.

4. Conclusion

Thymic neuroendocrine tumours causing ectopic ACTH secretion represent a rare but serious and potentially fatal cause of Cushing syndrome. Early recognition, systematic biochemical localisation, and functional imaging with Ga-68 DOTATATE PET-CT are essential for timely diagnosis and optimal surgical planning. Complete R0 resection via median sternotomy with lymphadenectomy is the only curative treatment and the most powerful determinant of long-term prognosis. The key learning points from this case are:

- Maintain a high index of clinical suspicion for ectopic ACTH syndrome in patients with florid, progressive cushingoid features, particularly when accompanied by opportunistic infections or unusual complications such as ocular involvement.
- Severe hypokalemia, metabolic alkalosis, markedly elevated ACTH, elevated urinary free cortisol ($>3 \times$ ULN), loss of diurnal cortisol variation, and non-suppressibility on HDDST are hallmarks of ectopic rather than pituitary-dependent Cushing syndrome.
- Ga-68 DOTATATE PET-CT is the gold-standard functional imaging modality for localising SSSTR-expressing thymic NETs and should

be performed in all patients with confirmed EAS and non-localised or ambiguous conventional imaging.

- WHO 2021 classification of thymic NETs (typical carcinoid, atypical carcinoid, LCNEC, SCC) guides prognostication; Ki-67 immunohistochemistry ($>20\%$ in this case) confirms Grade 2 NEC and informs post-operative surveillance strategy.
- Complete R0 resection via median sternotomy with mediastinal lymphadenectomy is the cornerstone of curative management. Empirical management of opportunistic infections concurrently with pre-surgical metabolic optimisation is essential to minimise perioperative morbidity.
- Long-term surveillance with biochemical markers (ACTH, cortisol, chromogranin A) and interval imaging is mandatory given the high recurrence rates of thymic NETs, even following R0 resection.

Declarations

Patient Consent: Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the journal's Editor-in-Chief upon request.

Conflicts of Interest: The authors declare no conflicts of interest relevant to this publication.

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diagnosis, management, data collection, and interpretation of findings. Gautam Katari contributed to conceptualization and manuscript drafting, while the other authors contributed to literature review and critical revision. All authors reviewed and approved the final manuscript and agreed to be accountable for all aspects of the work.

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