

Ectopic ACTH Syndrome With Association of Multiple Pulmonary Sclerosing Pneumocytomas and Multiple Carcinoid Tumorlets

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We present the case of multiple sclerosing pneumocytomas (SPs) associated with ACTH-secreting carcinoid tumorlets responsible for an ectopic Cushing syndrome (ECS). SP is a rare benign tumor originating from pulmonary epithelial cells. An 18-year-old male presented with shortness of breath and right-sided chest pain after exercise. Chest radiograph indicated right pneumothorax and bilateral lung nodules. CT imaging showed innumerable bilateral hypodense pulmonary nodules and a wedge resection gave the definitive diagnosis of SP with associated carcinoid tumorlets. Two years later, he presented with severe back pain in context of thoracic vertebral compression fracture. He had central fat accumulation, violaceous striae, proximal muscle weakness, hypertension, and diabetes. MRI of the pituitary gland showed a 7-mm adenoma. Inferior petrosal sinus sampling with no central-to-periphery gradient suggested an ectopic origin of ACTH, which was confirmed by ACTH expression in a subset of tumorlet cells in the lung lesions. The patient was started on ketoconazole and subsequently underwent a bilateral adrenalectomy. During follow-up, CT scans showed no growth of the lesions, except for the most recent CT scan, in which an increase in the size of the largest nodule was described. Ten years after the diagnosis, the patient remains asymptomatic of his pulmonary lesions. This article provides a case of ECS in the setting of multiple SP with associated carcinoid tumorlets.

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Sclerosing pneumocytoma (SP) is a rare benign tumor thought to originate from respiratory epithelial cells [1]. The etiology is not well understood. Most patients are asymptomatic at diagnosis and the tumor is found incidentally on screening chest radiographs [2]. Thoracotomy is indicated for a definite diagnosis, and surgical resection can be curative [3]. Lymph node metastasis is very rare and generally does not affect the favorable prognosis.

Abbreviations: BIPSS, bilateral inferior petrosal sinus sampling; CS, Cushing syndrome; EAS, ectopic ACTH syndrome; ECS, ectopic Cushing syndrome; IPS, inferior petrosal sinus; SCLC, small cell lung cancer; SP, sclerosing pneumocytoma.

Ectopic ACTH syndrome (EAS) is responsible for 10% to 15% of Cushing syndrome (CS) cases [4]. EAS is associated with endocrine and nonendocrine tumors, mainly bronchial carcinoid tumors and small cell lung cancer (SCLC). The biochemical diagnosis includes hypercortisolemia, high plasma ACTH, and a lack of cortisol suppression to dexamethasone and negative pituitary imaging. Inferior petrosal sinus (IPS) sampling permits calculation of gradient between the IPS and peripheral blood. We present the case of an 18-year-old male with CS with a small pituitary adenoma and multiple lung nodules, found to have ectopic production of ACTH by carcinoid tumorlets found within SP tumors, a rare entity combining multiple sclerosing hemangiomas with neuroendocrine lesions.

1. Case Report

An 18-year-old Hispanic male presented to the emergency room with shortness of breath and right-sided chest pain after exercise. Bilateral lung nodules were found on a chest radiograph (Fig. 1A). A CT scan showed multiple bilateral hypodense pulmonary nodules, the largest measuring 4.5×4.2 cm, and a 2.8×2.7 cm lesion with a cavitory component (Fig. 1C). A thoracostomy was performed and a wedge biopsy of the left upper lobe measuring $8.5 \times 6 \times 1.5$ cm showed multiple SPs with associated carcinoid tumorlets. Gross examination revealed numerous subpleural palpable nodules. On sectioning, they were well circumscribed, not encapsulated, solid nodules gray to tan-yellow. Microscopic examination showed multiple SPs associated with carcinoid tumorlets. The medium magnification of hematoxylin and eosin–stained image showed papillary pattern at the periphery and, predominantly, sclerosing pattern containing tubules of different shapes. These histoarchitectural patterns were present in all nodules. The papillae and tubules were lined by uniform columnar-to-cuboidal cells exhibiting the morphology of bronchial epithelium and activated type II pneumocytes.

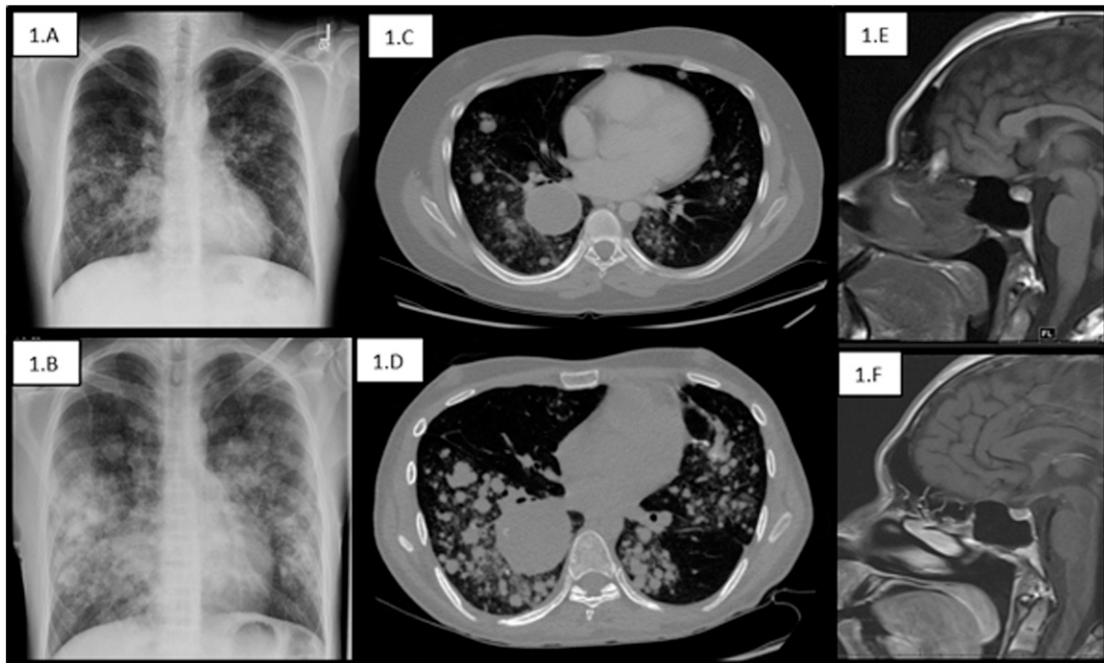


Figure 1. (A) Chest radiograph at diagnosis showing bilateral lung nodules. (B) Ten years later showing an increased number of bilateral lung nodules. (C) Multiple bilateral hypodense pulmonary nodules, the largest within the right lower lobe measures 4.5×4.2 cm. (D) Innumerable pulmonary nodules (10 years later) of different sizes throughout the lungs; the largest measures up to 5×5 cm. (E) Pituitary MRI: at diagnosis, a 7-mm hypoenhancing lesion present along the pituitary gland. (F) Pituitary MRI 10 years later. Relative diffuse hypoenhancement of the pituitary because of contrast bolus timing. Normal pituitary in size and contour.

The characteristic round cells were seen within the sclerotic area and showed focally clear cytoplasm. Immunostains were performed showing that the SP labeled for AE1/AE3 and TTF-1, showed equivocal labeling for TTF-1, and was negative for CD31, FLI1, chromogranin, and synaptophysin. The carcinoid tumorlet was positive for chromogranin and synaptophysin (Fig. 2E and 2F), focally positive for TTF-1, and negative for FLI1, and showed focal immunopositivity for ACTH (Fig. 2C).

A. In an Effort to Inhibit Angiogenesis, the Patient Was Treated With Thalidomide

Over the next 2 years, the patient gained >20 kg and developed central fat accumulation, facial puffiness, pedal edema, abdominal and axillary violaceous striae, and proximal muscle weakness. He presented with lower back pain and imaging studies that indicated a T12 compression fracture. A bone mineral density showed evidence of osteoporosis and treatment with bisphosphonates was started. His symptoms worsened, with increasing proximal muscle

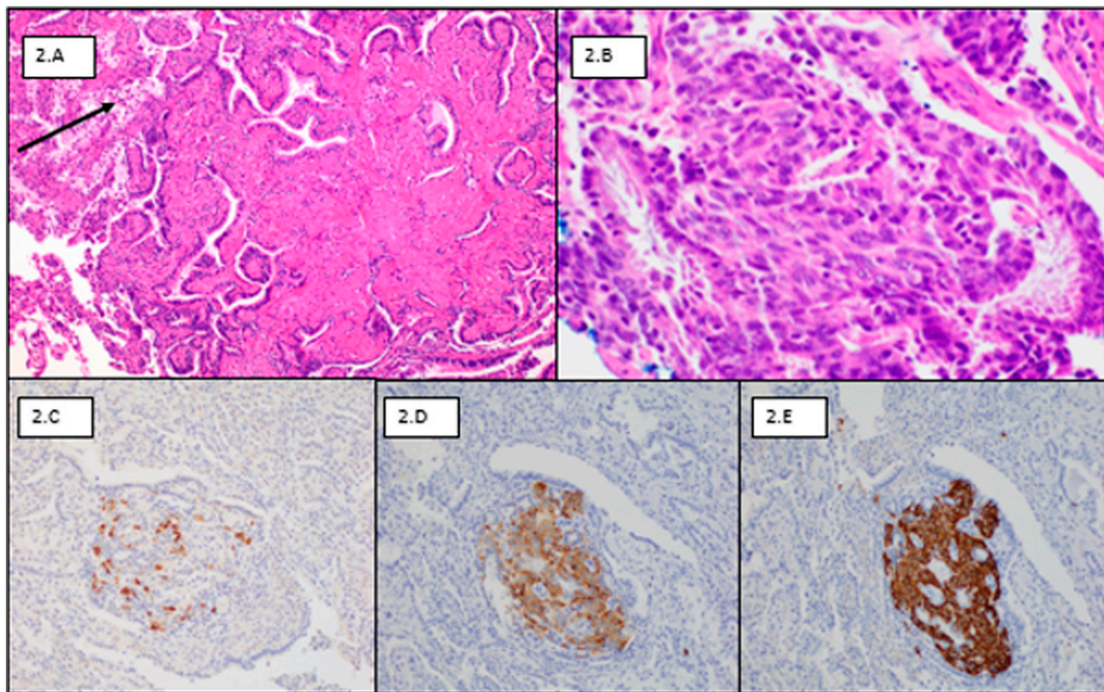


Figure 2. (A) Sclerosing pneumocytoma demonstrating a predominantly sclerotic pattern. Focal papillary pattern is seen at the periphery of the lesion and tubules of varying shape are embedded in the sclerotic background. The papillae and tubules are lined by uniform cuboidal cells and the less conspicuous but characteristic round cells are embedded in hyaline stroma. A focus of round cells with clear cytoplasm is also present (arrow) (hematoxylin and eosin, $\times 100$). (B) A high-magnification carcinoid tumorlet, which is composed of ovoid and spindle cells with a fair amount of cytoplasm and eccentrically located nuclei. The nuclei are predominantly uniform and the chromatin shows the characteristic “salt-and-pepper” appearance of neuroendocrine lesions (hematoxylin and eosin, $\times 400$). (C) Carcinoid tumorlet located within a sclerosing pneumocytoma. This relationship is well demonstrated in this medium magnification microphotograph. ACTH expression is present in 20% of the tumorlet cells (ACTH immunostain, $\times 200$), explaining the clinical presentation. (D) Immunostaining for chromogranin A shows cytoplasmic staining and confirms the histologic impression of a neuroendocrine nature in this carcinoid tumorlet (chromogranin A immunostain, $\times 200$). (E) Immunostaining for synaptophysin shows strong cytoplasmic staining, confirming the histologic impression of neuroendocrine nature of this carcinoid tumorlet (synaptophysin immunostain, $\times 200$). Origin of antibodies: chromogranin A, ready to use; clone 5H7 from Leica; synaptophysin, 1:2560, clone SNP88 from BioGenex; and ACTH, 1:1280, polyclonal from Thermo Scientific.

weakness and back pain, and he was admitted to the hospital, where he was diagnosed with hypertension and new-onset diabetes.

Laboratory data were consistent with excess of cortisol production, showing elevated 24-hour urinary free cortisol (8265 $\mu\text{g}/\text{d}$; normal range, $<50 \mu\text{g}/\text{d}$), plasma ACTH (112 pg/mL ; normal range, 7 to 50 pg/mL) and serum cortisol levels (39.1 $\mu\text{g}/\text{dL}$; normal range, 6.7 to 22.6 $\mu\text{g}/\text{dL}$). A 2-day high-dose dexamethasone suppression test indicated lack of suppression of serum cortisol (83.3 $\mu\text{g}/\text{dL}$), ACTH (101 pg/mL), and 24-hour urine free cortisol (3058 $\mu\text{g}/\text{d}$). After CRH administration, serum cortisol increased by 14% (from 46.0 to 52.5 $\mu\text{g}/\text{dL}$) and ACTH by 13% (from 83 to 94 pg/mL). MRI of the pituitary gland revealed a 7-mm central lesion (Fig. 1E).

The results of dynamic testing, along with a high 24-hour urinary free cortisol, hypokalemia, and rapid progression of his disease, indicated a high likelihood of ECS, which was confirmed when inferior petrosal sinus sampling failed to show a central-to-periphery gradient (baseline levels of ACTH ratio in IPS/periphery ranged from 0.8 to 1.20, and after CRH from 0.99 to 1.13).

B. The Patient Was Started on Ketoconazole Therapy for Elevated Cortisol Levels, Which Did Not Lower Even After Thoracotomy

In the setting of multiple nonresectable tumors and as a long-term solution for CS, the patient underwent a bilateral adrenalectomy and was started on hydrocortisone and fludrocortisone replacement. He was followed for 2 years after surgery and was then lost to follow-up. He presented 4 years later with dizziness and was admitted because of concern for adrenal crisis after discontinuing medications for 4 days. Symptoms resolved quickly with hormonal replacement of hydrocortisone and fludrocortisone. Ten years later from his initial presentation, the patient remains asymptomatic regarding his lung disease. Nevertheless, the last CT scan showed an interval increase in size and number of pulmonary lesions (Fig. 1D). The pituitary lesion, however, decreased in size over time (down to 5 mm), with an appearance suggesting a pars intermedia cyst that disappeared on the last MRI (Fig. 1F). ACTH levels on hydrocortisone replacement remained elevated ranging between 81 and 547 pg/mL .

2. Discussion

Ectopic ACTH secretion has been related to lung tumors such as SCLC and bronchial carcinoids. To our knowledge, a case of ECS secondary to an SP associated with carcinoid tumorlets has not been previously reported.

This rare tumor that was first described by Liebow and Hubbell in 1956 as a sclerosing hemangioma. In 2015 it was reclassified as an adenoma. Multiple studies have documented that SP is actually derived from primitive respiratory epithelial cells that express TTF-1 [1, 5, 6]. Most cases are solitary, with multiple SPs accounting for 3% to 4% of the cases.

A definite diagnosis is usually possible after postoperative histopathological examination. In our patient, it was made after a large wedge resection.

Macroscopically, SP is often well-defined measuring between 1 and 4 cm, with a tan or white appearance. Microscopically, it is mainly composed of cuboidal surface cells that tend to differentiate into type II pneumocytes and polygonal stromal cells, which have multiple differentiation potentials [1]. It is histologically characterized by the presence of hemorrhagic, papillary, solid, or sclerotic areas [2]. In our case, histological diagnosis showed multiple SPs with pneumocyte hyperplasia, and multiple carcinoid tumorlets within the tumor that expressed ACTH. This case documents ECS in the setting of SP with neuroendocrine lesions. The carcinoid tumorlets were positive for chromogranin and synaptophysin and focally positive for TTF-1 and ACTH. Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, another rare disorder, recognized as a preinvasive precursor to carcinoid tumors and tumorlets, has also been associated with CS. This disorder lacks, however, the characteristic features of SP, such as prominent sclerotization and vascularization as observed in our case.

Multiple cases identifying isolated scattered neuroendocrine cells or as a tumorlet within the center of SPs have been previously documented. It is not clear if primitive respiratory cells can differentiate toward a neuroendocrine phenotype or the presence of neuroendocrine cells represent hyperplastic structures induced by the tumor. These lesions, nevertheless, represent a minority among all cases of SP. Wang *et al.* [7] reported a similar case with multiple SP tumors along with multiple neuroendocrine tumorlets.

Complete surgical resection is curative and is the only effective treatment of SP [3]. Surgery could not be performed in this patient because of the extent of disease. Our case illustrates the clinical relevance of this association and the clinical evolution and behavior of SP over 10 years of follow-up in a patient with ECS postbilateral adrenalectomy.

Endogenous CS is usually ACTH-dependent in context of a pituitary adenoma. About 10% to 15% of CS cases are paraneoplastic from nonpituitary tumors secreting ACTH. Tumors in the lung are the most prevalent, including carcinoid tumors (30% to 46%) and SCLC (8% to 20%). Previous reports have documented immunopositivity for multiple hormones including ACTH, GH, calcitonin, and gastrin in SPs, previously called sclerosing hemangiomas [8]; however, to our knowledge, no cases of confirmed ECS have been reported to date. Our case confirms this association, demonstrates the synthesis of ACTH within the tumor leading to ECS, and adds further insight into the evolution of SP. The mechanisms leading to ectopic production of ACTH in a paraneoplastic syndrome are poorly understood. E2F1, independently of pituitary-specific Tpit/Pitx1, has been identified as a potential mediator of proopiomelanocortin expression in nonpituitary ACTH-producing tumor cells, and may represent a potential target for suppressing ACTH production in ECS [9].

In our patient, exogenous sources of glucocorticoids were excluded, and increased cortisol production was confirmed with a high 24-hour urinary free cortisol and high cortisol and ACTH levels. ACTH dependence was demonstrated by the markedly elevated ACTH levels. There was no response to high-dose dexamethasone test or CRH administration. MRI, however, showed a 7-mm pituitary mass. Nevertheless, simultaneous bilateral inferior petrosal sinus sampling (BIPSS) did not show a central-to-periphery gradient, confirming the suspicion of an ectopic origin of ACTH.

BIPSS is considered the gold standard to differentiate Cushing disease from the ectopic origin of ACTH. An inferior petrosal sinus-to-peripheral ACTH ratio >2 at baseline and >3 following CRH or desmopressin stimulation, confirms Cushing disease [10]. In our case, a pituitary lesion, measuring initially 7 mm, represented a diagnostic challenge. However, based on the nontypical aspect of a microcorticotroph adenoma, the high ACTH plasma levels, the absence of central-to-peripheral gradient on BIPSS, the diagnosis of EAS was made, which was then confirmed by the immunodetection of ACTH in the lung. The pituitary MRI showed no evidence of an adenoma 10 years after the initial symptoms, suggesting disappearance of a potential pars intermedia cysts. In addition, ACTH levels persisted elevated over time, making a central origin of ACTH unlikely. The optimal treatment of EAS is surgical resection of the corticotropin-secreting tumor when possible. In our patient, because of innumerable bilateral lung lesions, treatment of the primary tumor was not feasible, so initially an inhibitor of glucocorticoid synthesis such as ketoconazole was used. If all the treatments are ineffective or not tolerated, or in case of life-threatening hypercortisolemia, bilateral laparoscopic adrenalectomy can be performed [10]. In this case, symptoms improved with ketoconazole and complications did not progress rapidly, but an adrenalectomy was performed as a long-term solution given the patient's young age. During follow-up, CT scans showed no growth of the lesions, except for the most recent CT scan, in which an increase in the size of the largest nodule was described (Fig. 1D). Ten years after the diagnosis, the patient remains asymptomatic of his pulmonary lesions.

3. Conclusion

ACTH-dependent CS has been described in the setting of many tumors; this case of EAS secondary to multiple slowly growing pulmonary SPs with carcinoid tumorlets was followed

for 10 years. Our case also illustrates the diagnostic challenge and the role of BIPSS in the diagnostic workup in the presence of a pituitary lesion. Definitive therapy with bilateral adrenalectomy resulted in long-term solution of severe hypercortisolism in the setting of this unresectable pulmonary tumor.

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