CASE REPORT

Ectopic ACTH Cushing's syndrome caused by a large-cell neuroendocrine lung carcinoma responding to desmopressin

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Abstract

Ectopic adrenocorticotrophic hormone (ACTH) secretion (EAS) is a rare cause of ACTH-dependent Cushing's syndrome (CS), most often caused by a thoracic neuroendocrine tumor (NET). Large-cell neuroendocrine carcinomas (LCNEC) with EAS are rare and usually present a more severe ACTH secretion and hypercortisolism. We report a 44-year-old non-smoker man, who presented clinical and biochemical evidence of ACTH-dependent CS. Desmopressin 10 μg i.v. produced a 157% increase in ACTH and a 25% increase in cortisol from baseline; there was no stimulation of ACTH or cortisol during the corticotropin-releasing hormone (CRH) test and no suppression with high dose dexamethasone. Pituitary MRI identified a 5 mm lesion, but inferior petrosal venous sinus sampling under desmopressin did not identify a central ACTH source. Thorax and abdominal imaging identified a left lung micronodule. Surgery confirmed a lung LCNEC with strongly positive ACTH immunohistochemistry (IHC) in the primary and lymph node metastasis. The patient was in CS remission after surgery and adjuvant chemotherapy but developed a recurrence 9.5 years later, with LCNEC pulmonary left hilar metastases, ectopic CS, and positive ACTH IHC. This is the first report of LCNEC, with morphologic feature of carcinoid tumor of the lung with ectopic ACTH stimulated by desmopressin. Long delay prior to metastatic recurrence indicates relatively indolent NET. This case report indicates that response to desmopressin, which usually occurs in Cushing's disease or benign NETs, can occur in malignant LCNEC.

Key Words

- ectopic ACTH
- Cushing's syndrome
- bronchial neuroendocrine carcinoma
- desmopressin test

Learning points:

- Large-cell neuroendocrine carcinoma (LCNEC) of the lung is a rare cause of ectopic adrenocorticotrophic hormone secretion (EAS) causing paraneoplastic Cushing's syndrome.
- Desmopressin, CRH or dexamethasone suppression tests cannot completely distinguish Cushing's disease from EAS.
- The desmopressin test can be helpful in the differential diagnosis, localization and follow-up of pituitary corticotroph tumors, but clinicians should be aware that some, mostly benign NETs, can present positive responses to desmopressin.

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- Positive responses to the desmopressin test have been only rarely documented in malignant EAS tumors but were present in this case of LCNEC.
- Combining the desmopressin test with other dynamic tests, sellar MRI, inferior petrosal venous sinus sampling and thoraco-abdominal morphologic and functional imaging improves diagnostic accuracy.
- Long-term follow-up is required for patients with a history of resected LCNEC causing EAS, as recurrence can occur after a long delay.

Background

Ectopic adrenocorticotrophic hormone (ACTH) secretion (EAS) is a rare cause of ACTH-dependent Cushing's syndrome (CS), most often caused by a thoracic neuroendocrine tumor (NET) (Frete *et al.* 2020). The most common are well-differentiated bronchial NETs and small-cell carcinomas (Rekhtman 2022).

We describe a rare case of EAS from a large-cell neuroendocrine carcinoma (LCNEC) 'with morphologic features of carcinoid tumor' of the lung. Ectopic ACTH secretion was stimulated by desmopressin; metastatic recurrence and EAS developed 10 years later.

Case presentation

A 44-year-old non-smoker man presented with overt clinical CS rapidly progressive over 6 months, including hypokalemia, muscle weakness, weight gain, diabetes, hypertension, emotional lability and insomnia.

Morning ACTH was 50 pmol/L (normal: <11 pmol/L), cortisol was 1680 nmol/L (normal: <50 nmol/L) after 1 mg of dexamethasone suppression test (DST) and urinary free cortisol (UFC) was 35,297 nmol/24 h (normal: <789). MRI revealed a 5 × 3 mm pituitary lesion. Ketoconazole and metyrapone were administered to control hypercortisolism until referral to our center. Asymmetrical lower extremity edema was secondary to acute right venous popliteal thrombus, and chronic left femoral vein thrombus. Bilateral segmental and sub-segmental pulmonary emboli were also identified, for which he was anticoagulated.

Material and methods

ACTH was measured by immunoradiometric assay (ELSA-ACTH, Cisbio Bioassays, Codolet, France, coefficient of variability (CV) < 10%) and cortisol by chemiluminescent immunoassay (Siemens Healthcare Diagnostics Inc., CVs < 8%). For immunohistopathology (IHC), 4 µm sections were stained with ACTH antibody ready-to-use(RTU) (polyclonal, Ventana, Tucson, AZ, USA), on Ventana platform.

Investigation

During desmopressin 10 µg i.v. test, baseline cortisol was 1337 nmol/L, peaking 30 min later at 1675 nmol/L (25% increase); ACTH increased from 59.0 pmol/L to 151.9 pmol/L at 15 min post-injection (157% increase), Fig. 1). During 4 mg i.v. dexamethasone infusion over 4 h, cortisol was 1414 nmol/L at baseline, 1140 nmol/L 4 h after starting the infusion, and remained at 1587 nmol/L the next morning. Plasma ACTH fluctuated from 73.2 pmol/L basally to 60.6 pmol/L 10 h later (17% decrease) and 73.4 pmol/L the next morning. The next day, CRH, 1 µg/kg bolus i.v. did not stimulate ACTH: baseline of 57.3 and 58.7 pmol/L 15 and 45 min post-injection; similarly, baseline cortisol of 1682 nmol/L oscillated between 1503 and 1740 nmol/L. Inferior petrosal venous sinus sampling (IPSS) was performed using desmopressin 10 µg IV bolus which again produced an ACTH and cortisol increase in peripheral vein; a low central to peripheral ACTH gradient basally (<2) and of 1.7 on the right (<3 cutoff) post desmopressin was compatible with an ectopic source of ACTH (Table 1).

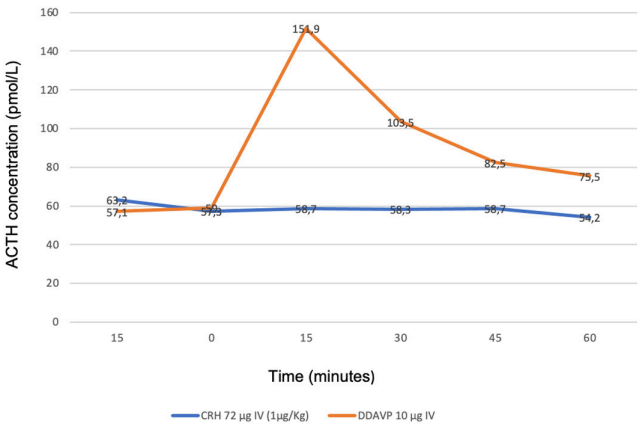

Figure 1
ACTH response to desmopressin and CRH tests.

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CT scans of the thorax and abdomen and initial indium-111 octreoscan did not identify the source of EAS but were difficult to interpret with the multiple bilateral pulmonary emboli. A PET scan did not reveal any highly FDG-avid tumor. Indium-111 octreoscan 2 weeks later identified a left inferior lung 3 mm nodule, previously interpreted as an emboli (Fig. 2A and B). This lesion was visible on a repeat angio CT scan and was compatible with an NET.

Treatment

A left inferior lung lobectomy revealed a 1.5 cm LCNEC, with morphologic features of carcinoid tumor (with positive chromogranin A staining) (Fig. 3A). Mitosis was high at 28–35 per high power field (HPF), and necrosis foci were rare (Fig. 3B). Two of 10 lymph nodes were positive for metastases (up to 1 cm). IHC was strongly positive for ACTH staining in the NET (Fig. 3C). Immediately after surgery, plasma ACTH and cortisol decreased rapidly, reaching nadirs of 3.7 pmol/L (lower limit of normal (LLN) = 2.0 pmol/L) and 71 nmol/L, respectively, in the following 48 h. The patient received hydrocortisone replacement.

Outcome and follow-up

The patient received four cycles of etoposide + platinol adjuvant chemotherapy. Hydrocortisone was slowly tapered and discontinued 21 months after the surgery. Yearly follow-up showed no symptoms or signs of CS and UFC and thoracic scans were normal. Plasma ACTH without hydrocortisone replacement fluctuated between 16.3 and 22.6 pmol/L (normal: <11 pmol/L). Nine years after surgery, the patient noticed muscle weakness, weight gain and a Cushingoid appearance. Morning ACTH was 56.9 pmol/L, morning cortisol was 633 nmol/L after 1 mg DST and UFC was 1717 nmol/24 h (normal: <789). A local recurrence with hypermetabolic, 14 × 11 mm left hilar lymph node was found in PET-DOTATATE scan, near the inferior lobectomy suture (Fig. 2C and D).

Table 1 Inferior petrosal venous sinus sampling before and after desmopressin 10 μg IV injection (0 time point), showing low central-to-peripheral ACTH gradient.

Time (min)	Right petrosal sinus ACTH (pmol/L)	Left petrosal sinus ACTH (pmol/L)	Peripheral plasma ACTH (pmol/L)	Plasma cortisol (nmol/L)
–5	67.7	62.9	51.6	1263
0	61.7	60.1	51.4	1337
3	82.1	82.1	54.4	1338
5	119.9	108.5	69.9	1304
10	133.6	130.8	99.3	1250
30	–	–	80.6	1475
45	–	–	69.0	1596
60	–	–	62.9	1586

A biopsy guided by an endobronchial ultrasound showed a recurrence of LCNEC.

A superior lobectomy with lymph node dissection was performed 9.5 years after initial lobectomy, revealing clusters of lymph node metastases and a separate left hilar lymph node metastasis of LCNEC (Fig. 4A) with extra nodal extension. IHC was again strongly positive for ACTH in the tumor tissues (Fig. 4B). In the left superior lobe of the lung, a 5.3 cm organized pneumonia was also found on pathology. Hydrocortisone replacement was initiated in view of postoperative suppression of ACTH and cortisol.

A PET-DOTATATE scan 6 months after surgery showed small, mildly active non-specific adenopathies in the superior portion of the left thorax region, in perivascular areas. A desmopressin test was performed, with no response of cortisol (basal 258 to peak 260 nmol/L) or of ACTH (basal 7.8 to peak 9.8 pmol/L). These imaging results were interpreted as reactive adenopathies, and the patient was considered in remission but remains in active surveillance.

Discussion

The main originality of this case report is that the ACTH-secreting malignant LCNEC of this patient was able to increase its ACTH secretion following desmopressin stimulation, while it was previously believed that only a minority of benign but not malignant NETs were able to respond to desmopressin. NETs represent only 2% or less of all primary lung tumors, and among those, LCNEC is an even rarer subtype, representing only 3% of all lung carcinomas (Rekhtman 2022). Similar to other lung cancers, LCNEC is more common in men and heavy smokers (Quinn *et al.* 2017). The histopathologic features of this patient's lung tumor exhibited carcinoid morphology but with mitotic counts exceeding 10 per 2 mm^2. According to the World Health Organization (WHO) thoracic pathology classification, a mitotic count of 10 per 2 mm^2 is the threshold for atypical carcinoids, and tumors exceeding it are classified as LCNEC; the literature regarding this borderline tumor group is scarce, but they are recognized as highly proliferative

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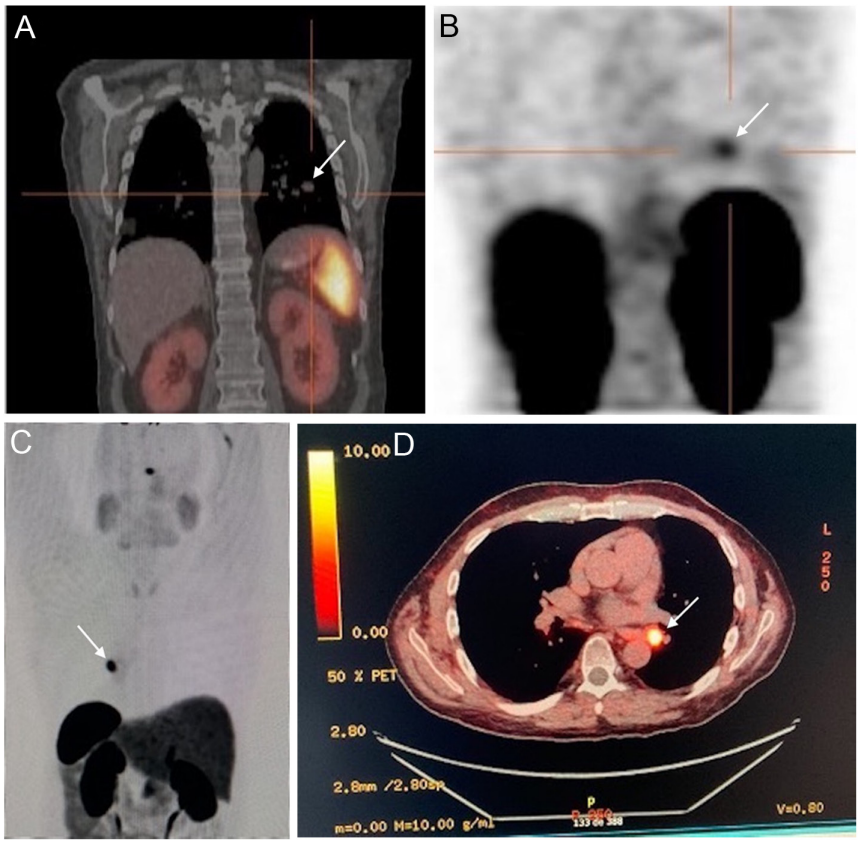

Figure 2
(A) CT scan of thorax demonstrating the left inferior lung lobe nodule (arrow). (B) Indium-111 octreoscan demonstrating uptake in the left inferior lung lobe nodule (arrow). (C) A PET-DOTATATE scan demonstrating the recurrence of LCNEC with a hypermetabolic, 14 × 11 mm left hilar lymph node lesion using gray scale (arrow). (D) A PET-DOTATATE scan demonstrating the recurrence of LCNEC lesion using color scale (arrow).

carcinoids, and 'an emerging variant' analogous to digestive grade 3 NETs (Rekhtman 2022). This category does not exist in the current thoracic WHO classification, but the current nomenclature for such tumors is 'LCNEC with morphologic features of carcinoid tumor', awaiting optimal classification as more data accumulate (Rekhtman 2022). Limited clinical data also support their similarity with differentiated NETs rather than NEC in terms of progression and response to therapy, but they can be highly aggressive, with 11 of 12 patients in one

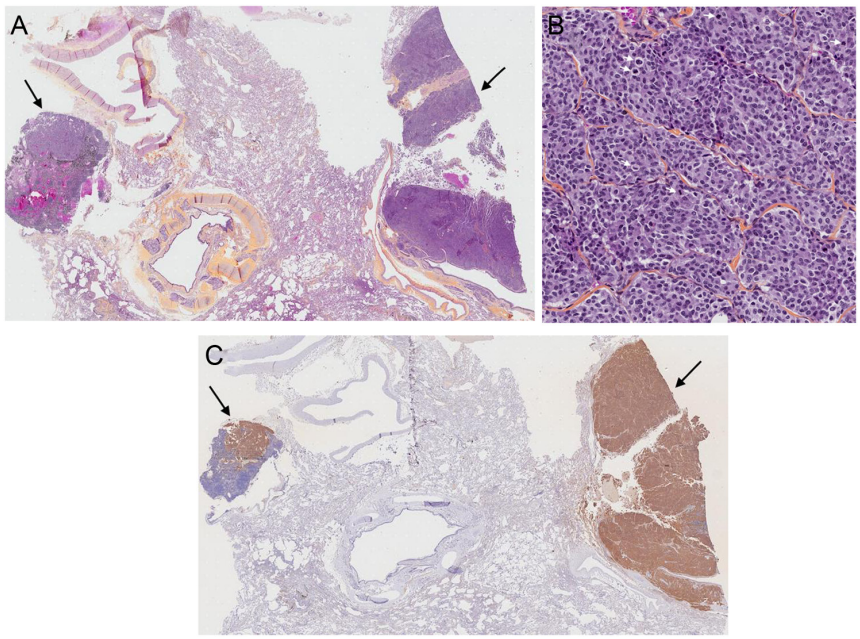

Figure 3
Histopathology of the LCNEC tumor recurrence at the left inferior lobectomy suture. (A) Predominantly endobronchial LCNEC tumor (right, arrow) with lymph node metastasis (left, arrow). Typical neuroendocrine architectural pattern with organoid features. Low power field (LPF) 5×, hematoxylin phloxine saffron stain. (B) Uniform polygonal cells with abundant amphophilic granular cytoplasm, round nuclei and salt and pepper chromatin. More than 5 mitotic figures are seen (white arrows). HPF (40×), hematoxylin phloxine saffron stain. (C) Tumor (right, arrow) and metastatic lymph node (left, arrow) at LPF 5× with diffuse and strong (brown color) ACTH expression (anti-ACTH stain).

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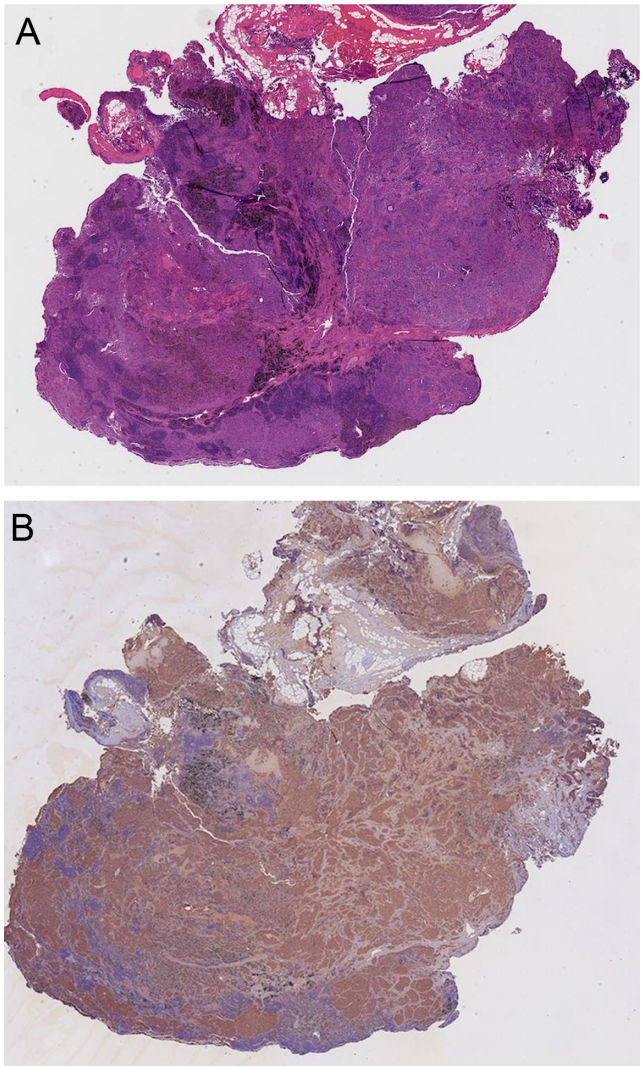

Figure 4
(A) Left hilar metastatic lymph node with extra nodal extension (LPF 5×, hematoxylin and eosin stain), demonstrating the recurrence of LCNEC. (B) Metastatic lymph node at LFP 5× with diffuse strong ACTH expression (anti-ACTH stain).

study developing post-surgical recurrence (Quinn *et al.* 2017, Rekhtman 2022).

The lack of suppression to high-dose dexamethasone and of stimulation by CRH suggested an ectopic ACTH-secreting poorly differentiated tumor. The desmopressin-responsive EAS, the positive octreoscan and the negative FDG-PET scan suggested a higher degree of cellular differentiation than in typical LCNEC; the latter can be sometimes so poorly differentiated that it can be mistaken for lung cancer adenocarcinoma or squamous cell carcinoma (Quinn *et al.* 2017).

Only three LCNECs causing EAS and CS have been reported previously (Lin *et al.* 2007, Verma *et al.* 2017, Qiang *et al.* 2021). Lin *et al.* described a 63-year-old man with metastatic lung LCNEC at presentation, overt CS, very elevated ACTH and cortisol concentrations and strong ACTH IHC staining of a metastasis (Lin *et al.* 2007). The second case, a 60-year-old male smoker with short history of progressive clinical CS and Horner syndrome, presented ACTH-dependent CS with normal sellar MRI; chest x-ray revealed a 5.5 cm left Pancoast tumor, suggesting EAS, with confirmed LCNEC and positive ACTH staining at pathology (5). The most recent case was a 64-year-old man presenting muscle weakness, hyperpigmentation and rhabdomyolysis due to severe hypokalemia; he had non-suppressible high ACTH and cortisol by high-dose dexamethasone, a normal pituitary MRI, negative IPSS and multiple hypermetabolic thoracic lymph nodes. Histopathology of the lymph nodes confirmed positive IHC ACTH staining of small-cell and LCNEC (Qiang *et al.* 2021). The first and last case were reported from China, and all three cases presented a short history of severe CS, evolving over 3 weeks (Lin *et al.* 2007, Verma *et al.* 2017, Qiang *et al.* 2021). A fourth case of LCNEC of the lung with ectopic ATCH expression was described by Bando *et al.* in 2020 (Bando *et al.* 2018), but in this case, the ectopic ATCH expression triggered paraneoplastic corticotroph auto-immunity with isolated ACTH deficiency instead of CS (Bando *et al.* 2018). Desmopressin testing was not performed in these four reported cases (Lin *et al.* 2007, Verma *et al.* 2017, Bando *et al.* 2018, Qiang *et al.* 2021).

Desmopressin is a synthetic vasopressin analog with higher specificity for vasopressin V2 receptors (AVPR2); it has several clinical indications but was used in our case as a dynamic test for the initial etiological diagnosis of ACTH-dependent CS and again during IPSS where a repeat peripheral stimulation of ACTH confirmed lack of central source of ACTH (Castinetti & Lacroix 2022).

Table 2 Characteristics of five patients with EAS and their response to desmopressin.

Patient's age/sex	EAS tumor	Baseline ACTH (pmol/L)	Desmopressin test result	CRH test result
67/male	Prostate cancer	55.0	–	–
28/female	Occult tumor	8.1	–	+
72/female	Breast cancer	17.6	–	–
72/male	Pancreatic carcinoid	50.6	+	+
72/female	Bronchial carcinoid	22.0	+	–

+Significant ACTH response; – no significant ACTH response.
Adapted from Terzolo and colleagues (2001).

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As the corticotroph tumors causing Cushing's disease (CD) express ectopic AVPR2 and overexpress V1b receptors (AVR1B) compared to normal corticotroph cells and most ACTH-secreting NETs, desmopressin stimulation has been used to help differentiate between normal axis, non-functional non-neoplastic hypercortisolism (pseudo-CS), CD and EAS (Castinetti & Lacroix 2022). No single dynamic test (desmopressin, CRH or high-dose dexamethasone) can distinguish these various conditions with 100% predictive value (Terzolo *et al.* 2001, Tsagarakis *et al.* 2002, Barbot *et al.* 2016, Frete *et al.* 2020). The majority of CD patients have positive responses to desmopressin, CRH and partial suppression with dexamethasone because most tumors express sufficient CRH, vasopressin or glucocorticoid receptors, while the majority of ectopic NET do not and fail to respond to those stimuli. However some, usually benign NETs, were shown to respond in a similar way to one or all three dynamic tests to patients with CD (Terzolo *et al.* 2001, Tsagarakis *et al.* 2002, Barbot *et al.* 2016, Frete *et al.* 2020). In the study by Terzolo *et al.*, two out five patients with EAS (40%) had a positive response to desmopressin stimulation (ACTH increase by at least 35% and >4.5 pmol/L, cortisol increase >20% and >193 nmol/L) (Terzolo *et al.* 2001); both tumors were carcinoid, and one was of bronchial origin (see details Table 2). In the study of Tsagarakis, ACTH increased by at least 50% in three out of five histologically confirmed cases of EAS, while 21 out of 26 cases of CD had a positive response (Tsagarakis *et al.* 2002). The same authors found AVPR2 mRNA in four out of four EAS tumors available for study and AVPR1b mRNA in three out of the four tumors (Tsagarakis *et al.* 2002). The positive desmopressin response of their patient with only AVPR2 mRNA and results of other mRNA studies done on carcinoid tumors with EAS combined with the high affinity of desmopressin for AVPR2 and low affinity for AVPR1b all suggest that the responsiveness of certain EAS tumors to desmopressin is due to the presence of AVPR2 (Tsagarakis *et al.* 2002).

Recent studies favor combined testing and a sequential approach to increase the sensitivity and specificity of dynamic tests and imaging tests to differentiate between CD and EAS. In a retrospective cohort of 170 patients of Barbot *et al.* in 2016, which included 21 patients with EAS, an ACTH increase of 32.4% over baseline after desmopressin injection had a specificity of 62% for CD (11). The specificity improved significantly if the desmopressin test was combined either with a high-dose dexamethasone suppression test or a CRH test (with pre-specified basal ACTH and cortisol changes) (Castinetti & Lacroix 2022). In 2020, Frete *et al.* proposed other combinations with improved specificity for CD and for EAS, based on results from a retrospective cohort of 167 patients, including 27 with EAS (Frete *et al.* 2020). If a pituitary MRI was negative, a CT scan was positive for a potential source of EAS, and both a desmopressin test and a CRH test were negative (less than 33% increase in ACTH and less than 18% increase in cortisol for the former), and then the negative predictive value for CD was 100% (Frete *et al.* 2020). Of note, the desmopressin test alone in the whole cohort had a sensitivity of 83% (95% confidence interval (CI) 76–88) and a specificity of 81% (95% CI 62–94) for the diagnosis of CD. Five patients with NETs had a positive response to desmopressin, and only one of these was from a malignant tumor, while all the others were well-differentiated bronchial NETs (Frete *et al.* 2020). Two of the latter had a positive response both to the desmopressin and to the CRH tests (Frete *et al.* 2020). While the combined imaging and dynamic testing approach can avoid up to 47% of IPSS testing (Frete *et al.* 2020), in our case, the discordant results between CRH and desmopressin testing, and the equivocal pituitary and thoracic scan with previous pulmonary emboli imaging results, required to do an IPSS to identify the source of ACTH.

In conclusion, the patient reported here is the fifth reported case of EAS caused by LCNEC of the lung with particular morphologic features of carcinoid; it is the first case in which the response to desmopressin and CRH was performed in a patient with lung LCNEC and EAS. While positive desmopressin responses have occasionally been described in well-differentiated bronchial NETs, our case report demonstrates that a positive response does not exclude a malignant origin. This particular LCNEC evolved slowly, recurring only 9.5 years after initial presentation and will require continued long-term follow-up. In this case, and in other desmopressin-responsive NETs, desmopressin stimulation testing should be repeated during follow-up, to see whether it can detect early recurrence, similar to what is recommended for CD (Castinetti & Lacroix 2022).

Declaration of interest
The authors have no disclosures related to this report and no competing interests to declare.

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Patient consent for publication
The patient provided an informed consent for the publication of this case report.

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Author contribution statement

SL wrote the first draft of the manuscript. RA performed the pathology studies and figures. DR performed the initial investigation and follow-up of the patient. AL performed the additional investigation and management of the patient and coordinated the case report. All authors reviewed and approved the final version of the manuscript.

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