CASE REPORT

Ectopic ACTH-producing large cell neuroendocrine Pancoast tumour presenting as Horner syndrome

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SUMMARY

We present an interesting case where a patient is presented with a droopy left eyelid (as part of Horner syndrome) and Cushingoid features which were a result of a Pancoast tumour (apical lung tumour in superior pulmonary sulcus) involving the left lung. This tumour was secreting ectopic adrenocorticotrophic hormone (ACTH), a paraneoplastic endocrine phenomenon, which resulted in Cushing syndrome symptomatology. Though most ectopic ACTH-producing lung cancers are either small cell or carcinoid tumours, this was in fact a large cell neuroendocrine cancer (LCNEC). Patient underwent surgical resection and adjuvant/neoadjuvant chemotherapy with radiation; however, he succumbed to LCNEC given aggressive nature of the disease.

BACKGROUND

Cushing syndrome due to ectopic adrenocorticotrophic hormone (ACTH) production is usually recognised as an endocrine paraneoplastic manifestation of small cell lung cancer or bronchial carcinoid; however, its association with large cell neuroendocrine cancer (LCNEC) is exceedingly rare. Horner syndrome due to a Pancoast tumour is a rare but classic presentation as well. To the best of our knowledge, this is the first case in recent medical literature where these two pathophysiologic phenomena (Horner syndrome from Pancoast tumour and ectopic ACTH production by LCNEC of lung) have together been identified in the same individual.

CASE PRESENTATION

A 60-year-old Caucasian man presented to his general practitioner with a 3-week history of fatigue, facial puffiness and a droopy left eye. He had seen an ophthalmologist 1 week before and was told to have normal visual acuity and no abnormality with cornea, anterior chamber, lens, posterior chamber or retina. Patient had noticed left facial and eyelid swelling for the last 3 weeks. His field of vision was reduced due to saggy eyelid at times giving him blurry vision. In addition, he had noticed generalised weakness with difficulty in walking. He had gained 25 lbs. of weight in the last 3 months.

Past medical history was significant for prostate cancer, hypertension, erectile dysfunction, left eye chalazion. Prior surgeries included a prostatectomy and tonsillectomy. Family history was significant for colon cancer in his mother, congestive heart failure and stroke in father, myocardial infarction and hypertension in his sister. Patient was a

long-time smoker smoking a half pack of cigarettes per day for 20 years. His prescription medication included lisinopril and hydrochlorothiazide.

Physical examination revealed normal vital signs except elevated blood pressure 146/92 mm Hg. Left upper eyelid was puffy, droopy and a lid lag was noticed. Strength in both lower extremities was 4/5 in all flexors and extensors and reflexes were normal. Rest of the physical examination was unremarkable. Laboratory testing showed sodium 147 mEq/L (normal: 135–145 mEq/L), potassium 3.0 mEq/L (normal: 3.5–5.5 mEq/L), fasting blood glucose 119 mg/dL, elevated white cell count 17 000/cu mm (normal: 4000–11 000/cu mm) with 89% neutrophils. MRI of orbit was performed to rule out any tumours which showed mild paranasal sinus mucosal thickening, unremarkable orbits and no ischaemia/infarct or abnormal orbital masses. Thyroid-stimulating hormone (TSH) was normal and prostate-specific antigen (PSA) was undetectable. Given presence of facial swelling, abnormal weight gain and hypokalaemia, general practitioner decided to check a 24-hour urinary free cortisol (UFC) while suspecting Cushing syndrome. His 24-hour free urinary cortisol came back elevated at 1185 µg/24 hour (normal <50); urine creatinine was 1.4 g/24 hour (normal 0.6–2.5).

INVESTIGATIONS

To confirm the diagnosis of Cushing syndrome, he was referred to endocrinology clinic. Three weeks later, he saw an endocrinologist who noticed that patient's swelling had extended to his feet, ankles, leg and abdomen. Patient had weakness in proximal muscles of arms and legs. Patient denied any oral or topical steroid intake. He denied use of any herbs or over-the-counter products containing steroids. In endocrinologist's clinic, his blood pressure was 172/100 mm Hg. Plethoric face, upper chest and minimal supraclavicular fat pads were noticed. There was no evidence of hyperpigmentation. Lower extremities showed 3/5 motor strength in hip flexors, 4/5 strength in proximal upper extremities. Confirmatory testing at endocrinologist's clinic showed a 24 hour free urinary cortisol of 1333 µg/24 hour, (normal 3.5–45), ACTH 152 pg/mL (normal 10–80), serum cortisol 38 (normal <15), dehydroepiandrosterone sulphate (DHEA-S) 1245 µg/dL (normal: 48–361), midnight salivary cortisol 667 ng/dL (normal <100) and 24-hour 5-hydroxyindoleacetic acid (5-HIAA) was 7.1 mg/24 hour (normal <8.1). He was initiated on furosemide for oedema and potassium supplementation for hypokalaemia. High-dose (8 mg)

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dexamethasone suppression test revealed a morning cortisol of 55 µg/dL (normal <5). Brain MRI did not show any evidence of sellar masses or pituitary tumour. Chest X-ray was ordered to look for ectopic ACTH production which showed a new pleural-based 5.5 cm × 3.5 cm left apical mass (figure 1). CT chest performed 4 days later confirmed the presence of a left-sided Pancoast tumour (figure 2, figure 3). He was suspected to have

Figure 1 Chest radiograph showing left upper lobe tumour (Pancoast) demarcated by a black arrow on postero-anterior view.

Figure 2 CT chest (coronal view) showing pleural-based Pancoast tumour marked by red arrow.

Figure 3 Axial CT scan chest showing 5.5 cm × 3.5 cm left upper lung tumour.

ectopic ACTH production due to Pancoast tumour causing Cushing syndrome. Patient was started on ketoconazole, metyrapone and mitotane and later spironolactone was added. As MRI brain was normal in the setting of an abnormal chest X-ray, it was decided not to do inferior petrosal sinus sampling for further workup for Cushing syndrome.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis in our case includes Cushing disease; however, given normal MRI brain, negative high-dose dexamethasone suppression test and abnormal chest radiograph showing lung tumour makes Cushing disease less likely.

TREATMENT

Patient was then referred to an oncologist who started him on neoadjuvant chemoradiation. Hypercortisolism and Horner syndrome responded well to adrenal enzyme inhibitors and neoadjuvant chemoradiation therapy. His serum cortisol decreased to 11.7 µg/dL, ACTH improved to 74 pg/mL, UFC came down to 16 µg/24 hour and Horner syndrome improved significantly. He was then sent to a thoracic surgeon for excision of left upper lobe mass. Patient underwent video-assisted thoracoscopic surgery (VATS) for removal of Pancoast tumour via left anterior thoracotomy (figure 4). Pathology from resected specimen was consistent with a poorly differentiated non-small cell lung cancer with large cell features and neuroendocrine differentiation (figure 5). Histopathology slides stained positively for synaptophysin, chromogranin, ACTH and thyroid transcription factor 1 (TTF-1) (figure 6, figure 7). Mucicarmin stain was

Figure 4 Gross tumour specimen following video-assisted thoracoscopic surgery (VATS) resection.

Figure 5 H&E stain (100×) showing neuroendocrine histomorphology with palisading and rosettes and large cell size with abundant cytoplasm.

Figure 6 Immunohistochemistry staining of the tumour showing positive stains for synaptophysin and chromogranin.

Figure 7 Immunohistochemistry staining of the tumour showing positive stains for adrenocorticotrophic hormone (ACTH) and thyroid transcription factor 1 (TTF-1).

negative. Based on histopathologic features and positive neuroendocrine histochemistry, a diagnosis of LCNEC of lung was made.

Patient was treated with cisplatin, etoposide and radiation therapy. Postoperatively, he developed new-onset atrial fibrillation with rapid ventricular response, respiratory failure and had to be intubated. Post-ICU stay was complicated with development of a left-sided pleural effusion which required insertion of a chest tube.

OUTCOME AND FOLLOW-UP

Patient was discharged to a skilled nursing facility after 7 days of hospital stay. After a 10-day stay at the nursing facility, he developed new-onset low back pain, left foot drop and acute confusion. MRI brain was repeated which showed several new lesions in right frontal cortex, cerebral hemispheres and cerebellum. Oncologist recommended palliative radiation though patient and family members chose hospice care and comfort measures at that point. Patient expired 1 week later.

DISCUSSION

This case is interesting due to the combination of two phenomena occurring in the same patient:

- Pancoast tumour causing Horner syndrome;
- ectopic ACTH production/Cushing syndrome caused by large cell (non-small cell) neuroendocrine tumour.

Pancoast tumour causing Horner syndrome

Pancoast tumour is the name given to apical lung tumours which arise in the superior pulmonary sulcus. They may cause Horner syndrome (ptosis, miosis, anhidrosis and enophthalmos) due to their involvement of the cervical sympathetic plexus (second-order neuron).¹ Horner syndrome can result from a lesion anywhere along a three-neuron sympathetic pathway comprising of central, preganglionic and postganglionic neurons; these neurons are also known as the first-order, second-order and third-order neuron, respectively. The second-order (preganglionic) neuron starts at the level of T1 in the spinal cord and then goes over the lung apex in the form of cervical sympathetic

plexus and then finally culminates at the superior cervical ganglion at C3–C4 level near bifurcation of the common carotid artery.² Ptosis results from paralysis of Muller muscle which is supplied by sympathetic pathway and is responsible for minor upper lid elevation and lower lid retraction. Anhidrosis is present only in central and preganglionic lesions and is absent in postganglionic lesions as sympathetic fibres involved in sweat production diverge at superior cervical ganglion.² Second-order neuron Horner syndrome can be caused by apical lung tumours (Pancoast) as seen in our case, mediastinal tumours, cervical rib, subclavian artery aneurysm, thyroid malignancies or iatrogenic causes (eg, central line or chest tube insertion, thoracic surgery).²

Treatment of Horner syndrome depends on its underlying cause and may require resection of the underlying tumour (eg, VATS was needed for removal of Pancoast tumour in our patient), rib, aneurysm repair or correction of iatrogenic conditions.

Ectopic ACTH production/Cushing syndrome caused by LCNEC

Cushing syndrome can be caused by ACTH-dependent, ACTH-independent and miscellaneous (iatrogenic, factitious, pseudo-Cushing) factors. Ectopic ACTH production is ACTH dependent and second most common ACTH-dependent cause of Cushing syndrome. Ectopic production of corticotropin-releasing factor (CRF) by a tumour can cause ectopic ACTH production resulting in Cushing syndrome as well. Clinical manifestations of Cushing syndrome are similar regardless of the underlying cause though hyperpigmentation is more common in ectopic ACTH production.

Ectopic ACTH production is an endocrine paraneoplastic syndrome which is usually associated with small cell lung cancer, bronchial carcinoid, lung adenocarcinoma/squamous cell carcinoma and other neuroendocrine tumours (eg, gastrinoma, pancreatic islet, medullary thyroid carcinoma, pheochromocytoma, etc) though its association with LCNEC is exceedingly rare.³ Some of the other paraneoplastic syndromes associated with LCNEC include acromegaly, encephalitis and carcinoid syndrome.

Metabolic manifestations of ectopic ACTH syndrome include hypertension, hypokalaemia, fluid retention and oedema, metabolic alkalosis and hyperglycaemia. In addition to the excess

mineralocorticoids produced by ACTH stimulation of the adrenal gland, high levels of cortisol exert activity through the mineralocorticoid receptor and lead to severe hypokalaemia.⁴ Extremely elevated UFC, elevated plasma ACTH concentration, presence of hypokalaemia and rapid onset of hypercortisolism all favour the diagnosis of ectopic ACTH secretion.⁵

Ectopic ACTH production by a tumour can be detected by performing a CT, MRI, positron-emission tomography (PET) or octreotide scintigraphy scan. Treatment of ectopic ACTH production syndrome is by surgical removal of the causative tumour. For patients with non-resectable tumours, hypercortisolism is controlled with adrenal enzyme inhibitors such as ketoconazole, metyrapone or etomidate as in our case (figure 8).⁶ Mitotane has also been used to achieve medical adrenalectomy. Glucocorticoid antagonist mifepristone may be used to treat hyperglycaemia caused by hypercortisolism and somatostatin analogue octreotide has been used to reduce ectopic ACTH secretion in some cases.⁶

LCNEC is a type of neuroendocrine tumour that can affect lungs, gall bladder,⁷ urinary bladder,⁸ head and neck,⁹ prostate,¹⁰ ovary,¹¹ uterine cervix,¹² vagina,¹³ endometrium,¹⁴ breast,¹⁵ colon,¹⁶ ileum,¹⁷ rectum,¹⁸ bile ducts,¹⁹ stomach,²⁰ renal pelvis,²¹ skin,²² thymus,²³ etc. Pulmonary neuroendocrine tumours make up to 20% of all lung cancers of which LCNEC are 10% (ie, 2–3% of all lung cancers). Like many other forms of lung cancers, smoking is a known risk factor for LCNEC as well. There seems to be a predilection for male sex with median age of diagnosis around 64 years.²⁴ LCNEC is a high-grade malignant tumour. Diagnosis of LCNEC is based on neuroendocrine morphology and positive neuroendocrine marker immunohistochemistry. Fine needle aspiration/small biopsies are often insufficient to make the diagnosis of LCNEC and so it is not uncommon that the diagnosis may be made after gross resection of the tumour. As per WHO 2004 and 2015 lung tumour classification criteria, demonstration of at least one neuroendocrine marker is required for the diagnosis of LCNEC. Most LCNEC (up to 70%) stain positively for synaptophysin and chromogranin A. TTF-1 is expressed in ~50% of LCNEC.²⁵

Given the rarity of this tumour, randomised control trials are not available and so treatment principles for LCNEC have been borrowed from small cell lung cancer. Thoracotomy/VATS is the

Figure 8 Steroidogenesis sketch showing steroid inhibitors and their sites of action. Enzymes depicted in dashed rectangles. Adrenal enzyme inhibitors shown in green rounded rectangles.

standard approach for surgical resection of the tumour. LCNEC of the lung usually presents as a peripheral lesion than a central tumour. Platinum-based adjuvant chemotherapy along with etoposide is the most common chemotherapeutic treatment regimen.²⁴ Adjuvant radiotherapy may also be used. Preoperative or neoadjuvant chemotherapy is rarely employed. LCNEC has a poorer prognosis than other neuroendocrine tumours involving the lung with 5-year overall survival rate for LCNEC being ~28% (range 20–40%).²⁴

Learning points

- ▶ Large cell neuroendocrine cancer (LCNEC) is a rare cause of ectopic adrenocorticotrophic hormone (ACTH) production/ Cushing syndrome (paraneoplastic endocrine phenomenon).
- ▶ Pancoast tumour is a rare yet classic presentation of second-order Horner syndrome.
- ▶ Surgical resection of tumour (if possible) is the mainstay of treatment for LCNEC.

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REFERENCES

- 1 Husain AN. Lung. In: Kumar V, Abbas AK, Aster JC. *Robbins basic pathology* 9e. Philadelphia: Elsevier Saunders, 2013:505–14.
- 2 Kedar S, Bioussé V, Newman NJ. Horner Syndrome. In: UpToDate. Brazil PW. ed. *UpToDate*. Wolters Kluwer, Waltham, MA (accessed 22 Dec 2016)
- 3 Lin CS, Yao NS, Cheng MF, et al. Ectopic ACTH syndrome associated with large-cell neuroendocrine carcinoma of the lung. *Am J Med Sci* 2007;334:487–9.
- 4 Jameson J, Longo DL. Paraneoplastic Syndromes: Endocrinologic/Hematologic. In: Kasper D, Fauci A, Hauser Set al. eds. *Harrison's principles of internal medicine*, 19e. New York, NY: McGraw-Hill, 2015. <http://accessmedicine.mhmedical.com/content.aspx?bookid=1130&Sectionid=79730822> (accessed December 22, 2016).
- 5 Nieman LK. Establishing the cause of Cushing's syndrome. In: UpToDate. Lacroix A. ed. *UpToDate*. Wolters Kluwer, Waltham, MA (accessed 22 Dec 2016).
- 6 Nieman LK. Overview of the treatment of Cushing's syndrome. In: UpToDate, Lacroix A. ed. *UpToDate*, Wolters Kluwer, Waltham, MA (accessed 22 Dec 2016).
- 7 Buscemi S, Orlando E, Damiano G, et al. "Pure" large cell neuroendocrine carcinoma of the gallbladder. Report of a case and review of the literature. *Int J Surg* 2016;28:S128–32.
- 8 Gupta S, Thompson RH, Boorjian SA, et al. High grade neuroendocrine carcinoma of the urinary bladder treated by radical cystectomy: a series of small cell, mixed neuroendocrine and large cell neuroendocrine carcinoma. *Pathology* 2015;47:533–42.
- 9 Thompson ED, Stelow EB, Mills SE, et al. Large cell neuroendocrine carcinoma of the head and neck: a clinicopathologic series of 10 cases with an emphasis on HPV status. *Am J Surg Pathol* 2016;40:471–8.
- 10 Okoye E, Choi EK, Divatia M, et al. De novo large cell neuroendocrine carcinoma of the prostate gland with pelvic lymph node metastasis: a case report with review of literature. *Int J Clin Exp Pathol* 2014;7:9061–6.
- 11 Asada K, Kawana K, Teshima S, et al. Poor prognosis of ovarian cancer with large cell neuroendocrine carcinoma: case report and review of published works. *J Obstet Gynaecol Res* 2014;40:869–72.
- 12 Nagao S, Miwa M, Maeda N, et al. Clinical features of neuroendocrine carcinoma of the uterine cervix: a single-institution retrospective review. *Int J Gynecol Cancer* 2015;25:1300–5.
- 13 Jin B, Pickens A, Shah MB, et al. Primary large cell neuroendocrine carcinoma of the vagina: cytomorphology of previously unreported case. *Diagn Cytopathol* 2010;38:925–8.
- 14 Pocrnich CE, Ramalingam P, Euscher ED, et al. Neuroendocrine carcinoma of the endometrium: a clinicopathologic study of 25 cases. *Am J Surg Pathol* 2016;40:577–86.
- 15 Okoshi K, Saiga T, Hisamori S, et al. A case of cytokeratin 20-positive large-cell neuroendocrine carcinoma of the breast. *Breast Cancer* 2012;19:360–4.
- 16 Xu F, Feng GS, Wang ZJ, et al. Synchronous double cancers of colonic large cell neuroendocrine carcinoma and gastric squamous-cell carcinoma: a case report and review of literature. *Int J Clin Exp Pathol* 2014;7:5177–80.
- 17 Wang X, Li Y, Feng H, et al. Large cell neuroendocrine carcinoma of the ileocecal junction with well differentiation adenocarcinoma. *Neuro Endocrinol Lett* 2015;36:133–5.
- 18 Muto M, Ichiki K, Muto M, et al. [A case of large cell neuroendocrine carcinoma of the rectum]. *Nihon Shokakibyo Gakkai Zasshi*. 2015;112:683–9.
- 19 Sasatomi E, Nalesnik MA, Marsh JW. Neuroendocrine carcinoma of the extrahepatic bile duct: case report and literature review. *World J Gastroenterol* 2013;19:4616–23.
- 20 Fujimura Y, Nakahara O, Otao R, et al. [A case of large cell neuroendocrine carcinoma of the stomach with liver metastasis effectively treated with S-1 and CDDP combination therapy]. *Gan To Kagaku Ryoho* 2014;41:369–71.
- 21 Palumbo C, Talso M, Dell'Orto PG, et al. Primary large cell neuroendocrine carcinoma of the renal pelvis: a case report. *Urologia* 2014;81:57–9.
- 22 Nagase K, Kimura H, Yonekura N, et al. Large-cell neuroendocrine carcinoma of the skin: ultrastructural and immunohistochemical findings. *J Cutan Pathol* 2016;43:1067–73.
- 23 Ose N, Inoue M, Morii E, et al. Multimodality therapy for large cell neuroendocrine carcinoma of the thymus. *Ann Thorac Surg* 2013;96:e85–7.
- 24 Filosso PL, Rena O, Guerrero F, et al. Clinical management of atypical carcinoid and large-cell neuroendocrine carcinoma: a multicentre study on behalf of the European Association of Thoracic Surgeons (ESTS) Neuroendocrine Tumours of the Lung Working Group†. *Eur J Cardiothorac Surg* 2015;48:55–64.
- 25 Rekhtman N. Neuroendocrine tumors of the lung: an update. *Arch Pathol Lab Med* 2010;134:1628–38.

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