Mucoepidermoid lung carcinoma causing ectopic Cushing’s syndrome

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Abstract

Introduction
We are not aware of any reports of ectopic Cushing’s syndrome caused by adrenocorticotropic hormone (ACTH) precursors secreting mucoepidermoid lung carcinoma. We present a rare case of a patient who was diagnosed with Cushing’s syndrome caused by mucoepidermoid lung carcinoma which occurred 18 years after the resection of mucoepidermoid carcinoma of trachea and ectopically secreted ACTH precursors.

Case report
We present a 43-year-old male patient who was operated for tracheal mucoepidermoid carcinoma when he was 25 years old (in 1993). In October 2011, he presented with Cushing’s syndrome. He was hyperpigmented, he had new-onset hypertension, frank peripheral oedema, hyperglycaemia, hypokalemic alkalosis and leukocytosis. His cortisol level after 2-day dexamethasone suppression test was 2033 nmol/l, he had a normal level of ACTH (7.06 pmol/l; n. <10.2 pmol/l), but a markedly elevated level of ACTH precursors (520 pmol/l; n. <40 pmol/l)). We found a large tumour mass (15 cm diameter) in the right hemithorax. After debulking surgery and introduction of metyrapone therapy 2-day, ketoconazole was added to therapy and radiotherapy was planned. However, the patient died 6 months after the first presentation.

Conclusion
In this case report, we illustrate diagnostic and therapeutic challenges in an unusual situation of ACTH precursors secreting mucoepidermoid lung carcinoma, which occurred 18 years after the resection of mucoepidermoid carcinoma of trachea.

Introduction
Mucoepidermoid carcinomas (MECs) originate from glandular tissue identified with salivary glands located in the submucosa of the trachea and bronchus. These are very rare tumours, as they compose only 0.1–0.2% of all lung cancers. There are very few reports of MEC causing ectopic Cushing’s syndrome (ECS). It is generally assumed that ECS is caused by ACTH. However, there is some significant evidence that ectopic tumours can secrete ACTH precursors, mostly proopiomelanocortin (POMC) and pro-ACTH. It was established that in patients with ECS, the level of ACTH precursors, rather than the level of ACTH itself, correlates with the serum cortisol level. The first line of treatment of ECS is surgical: resection of primary tumour or bilateral adrenalectomy or a combination of both. However, when surgical treatment for severe ECS is not feasible, medical therapy should be introduced. Commonly, steroidogenesis inhibitors ketoconazole and metyrapone are used. Occasionally, mitotane, metyrapone and ketoconazole combination therapy are used as an alternative to bilateral adrenalectomy. Currently accepted optimal treatment for MEC is complete resection of primary tumour, when achievable, and postoperative mediastinal radiation therapy. This article reports a case of mucoepidermoid lung carcinoma causing ECS.

Case report
In October 2011, a 43-year-old man presented with a 2-week history of facial and peripheral oedema. The patient also complained about hyperpigmentation, which was most prominent on his knuckles. He had put on 8 kg without changing his nutritional habits. In his personal history, there was an operation of MEC of trachea 18 years earlier. He had been a smoker of 10 cigarettes per day for about 25 years.

The clinical examination revealed elevated blood pressure (systolic 185; diastolic 95 mmHg) and prominent cushingoid features, including central obesity (weight 133.9 kg, height 189 cm, BMI 37), moon facies, buffalo hump, muscle atrophy and hyperpigmentation.

Laboratory results were significant for hypokalemic metabolic alkalosis (serum potassium 2.87 mmol/l, pH 7.51), leukocytosis (Lkc 18.1 × 10⁹/l) with neutrophilia (16.5 × 10⁹/l) and new-onset hyperglycaemia (fasting serum glucose 7.2 mmol/l).

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Endocrine assessment showed absent circadian variation in cortisol secretion (8H 1791 nmol/l, 16H 1702 nmol/l, 24H 1487 nmol/l) and failure of cortisol suppression (cortisol after 1 mg dexamethasone suppression [DST] test 1448 nmol/l and after 48-h 2 mg/day DST 2033 nmol/l). Plasma ACTH level was unsuppressed (7.06 pmol/l; n. <10.2 pmol/l), indicating the presence of ACTH-dependent Cushing’s syndrome. To differentiate between the more prevalent ACTH pituitary adenoma (Cushing’s disease) and ECS, we first performed a pituitary MRI, which was unremarkable. There was no suppression of cortisol after 48-h 8 mg DST (2191 nmol/l). We might have considered performing inferior petrosal sinus sampling (IPSS) if the chest X-ray had not revealed a very large tumour mass in the right hemithorax, which was confirmed with the chest computed tomography (CT) later on (Figure 1). To establish the nature of the tumour, bronchoscopy was performed, but the results were inconclusive, as the biopic samples predominantly contained necrotic tissue. A negative octreotide scan excluded the presence of somatostatin receptors on the tumour cell surface. Positron emission tomography scan showed a large tumour mass (15.5 × 14.5 × 13.5 cm) with central necrosis involving the right lower lung lobe and metastases in the mediastinal and right supraclavicular lymph nodes (Figure 2). A debulking surgery was planned. To improve the patient’s condition and diminish the effects of hypercortisolism on serum potassium and blood pressure, metyrapone was introduced.

With metyrapone 500 mg four times a day (q.d.s.), the cortisol level was 1048 nmol/l. Right lower lobectomy was performed. After the surgery morning, the cortisol level fell to 566 nmol/l (with metyrapone 250 mg q.d.s.) and the basal ACTH level to 3.57 pmol/l.

The pathohistological result showed MEC with intermediate-to-low degree of differentiation and with focal neuroendocrine secretion. Immunohistochemistry was focally positive for ACTH. Mitotic activity was 3–4 mitoses per high-power field (HPF) or 12 mitoses per mm$^2$. The morphologic and immunophenotypic re-evaluation of the biopsy of the tracheal tumour from 1993 revealed better morphologic differentiation and lower mitotic activity (1 mitosis per HPF). Electronic microscopy showed glandular differentiation without neuroendocrine markers and no ACTH secretion.

In less than a month after the operation, the cortisol and ACTH levels started to rise again (cortisol 1018 nmol/l with metyrapone 750 mg t.i.d. and ACTH 6.15 pmol/l). As from the very beginning the serum level of ACTH was relatively low in contrast to high levels of cortisol and prominent cushingoid features, the level of ACTH precursors was determined. This was done at the Manchester University where measuring of ACTH precursors is possible. The level of ACTH precursors was frankly elevated to 520 pmol/l (normal level <40 pmol/l), as we expected.

Unfortunately, the follow-up CT scan performed soon after biochemical deterioration showed progression of mediastinal and supraclavicular metastases. Early reoperation for metastasectomy was performed and radiotherapy was planned.

After reoperation, the patient’s condition improved again. The cortisol level dropped to 98 nmol/l while the patient was on therapy with ketoconazole 400 mg three times a day (t.i.d.) and metyrapone 500 mg t.i.d. However, only 1 month after the reoperation, the patient’s condition deteriorated. The level of cortisol rose to 2039 nmol/l with ketoconazole.
Tumour imaging with 18F-FDG PET/CT. A tumour mass with central necrosis in the right lower lung lobe; 2: metastases in mediastinal lymph nodes; 3: metastases in right supraclavicular lymph nodes; 4: high 18F-FDG uptake by the adrenal glands.

Figure 2: Tumour imaging with 18F-FDG PET/CT. 1: a tumour mass with central necrosis in the right lower lung lobe; 2: metastases in mediastinal lymph nodes; 3: metastases in right supraclavicular lymph nodes; 4: high 18F-FDG uptake by the adrenal glands.

400 mg t.i.d. and metyrapone 750 mg t.i.d. We continued with symptomatic therapy, which was supposed to maintain the patient's condition until radiotherapy. Unfortunately, the patient died 6 months after the presentation, even before the radiotherapy could have been applied.

Discussion

The current knowledge about ECS is limited and is acquired mostly from literature reviews, series reports from large institutions and individual case reports. It is estimated that ECS constitutes 8% to 18% of all causes of Cushing's syndrome. Prevalence of tumours that usually cause ECS differs among reports, with most of them considering small-cell lung carcinoma, bronchial and thymic carcinoids the most common.

We are not aware of any reports of MEC causing ECS. However, there was a case of MEC of trachea causing ECS in a case series from Aniszewski et al. Our patient first had MEC of trachea at the age of 25. We did not have the information of presence of Cushing’s syndrome at that time as he was only operated on without any endocrine evaluation. The tumour recurred as a MEC of pulmonary parenchyma 18 years later. Pathohistological result of our patient's tumours suggests that tracheal mucoepidermoid tumour in 1993 was a low-grade variant with a relatively high level of differentiation and without neuroendocrine secretion. On the other hand, the subsequent tumour appeared to be poorly differentiated with a high proliferation index and a focal neuroendocrine secretion of ACTH-like peptide. Nevertheless, the basic morphological structure and immunophenotypic profile of both tumours were similar. Therefore, we cannot exclude the possibility of MEC of trachea metastasising to the lungs, as both lymphangitic and haematogenous metastases have been demonstrated for MECs.

However, it seems rather unlikely that metastasis would have occurred only after 18 years.

The diagnosis of ECS is often challenging. Today, the golden standard test for distinguishing Cushing’s disease from ECS is IPSS, which has a very high sensitivity (95%) and specificity (100%). However, the IPSS is an invasive procedure with potential risk for serious complications and is limited also by the availability of an experienced neuroradiologist. The measurement of ACTH precursors was suggested as a diagnostic test which can with a cut-off value of 100 pmol/l distinguish between Cushing’s disease (<100 pmol/l) and ECS (≥100 pmol/l) with 100% specificity and 93% sensitivity.

In our patient, the level of ACTH precursors—but not the level of ACTH itself—correlated with plasma cortisol, which is typical of patients with ECS.

The treatment of both MEC and of ECS is demanding. ECS is usually treated surgically either by resection of the primary tumour or by bilateral adrenalectomy or else by combined bilateral adrenalectomy along with the primary tumour resection. To control cortisol overproduction, medical therapy is commonly introduced. In a retrospective review from Ejaz et al., ketoconazole and metyrapone were used in 93% of patients. In patients with Cushing’s disease, the success rate of ketoconazole treatment is reported to be 80% (dosing 600–1200 mg/day) and of metyrapone 75% (dosing 750–6000 mg/day). There is little data on the benefit of ketoconazole treatment in patients with ECS. It was estimated that ketoconazole is effective in 50% of patients with ECS. Metyrapone and ketoconazole frequently fail to control Cushing’s syndrome, either because ACTH overrides their cortisol-blocking actions or because of intolerable side effects. In our patient, ketoconazole and metyrapone

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ameliorated hypercortisolemia for a relatively short time. This could have been due to the escape phenomenon posed by two steriodogenes inhibitors, but more probably it was due to the rapid progression of the disease. One could also speculate that the dose of metyrapone was sub-optimal, but a higher dose was not tolerated by the patient.

The treatment of hypercortisolism in our patient was necessary. However, only the treatment of MEC, when achievable, would have been a real solution for him. Case series agree that the complete surgical resection provides patients with the best chance of long-term survival. Postoperative mediastinal radiation is now the accepted adjuvant therapy. The role of preoperative, neoadjuvant radiotherapy has not been explored. There is no defined role for chemotherapy in glandular tumours.

In our patient, complete surgical resection was not possible as the tumour had already metastasised to mediastinal and extrathoracic lymph nodes. Debulking surgery resulted in significant, but transient clinical and biochemical improvement, and radiation therapy was planned. Due to rapid growth of metastases, an early reoperation was needed. Its benefit was only short-lived again, and soon the succession of infections worsened the patient’s condition. The patient died 6 months after the first presentation. Debulking surgery resulted in significant, but transient clinical and biochemical improvement, and radiation therapy was planned. Due to rapid growth of metastases, an early reoperation was needed. Its benefit was only short-lived again, and soon the succession of infections worsened the patient’s condition. The patient died 6 months after the first presentation.

Conclusion
In this case report, we illustrate diagnostic and therapeutic challenges in an unusual situation of ACTH precursors secreting mucoepidermoid lung carcinoma, which occurred 18 years after the resection of MEC of trachea.

Abbreviations list
CT, computed tomography; DST, dexamethasone suppression test; ECS, ectopic Cushing’s syndrome; HPF, high-power field; IPSS, inferior petrosal sinus sampling; MEC, mucoepidermoid carcinoma; POMC, proopiомelanocortin; q.d.s., four times a day; t.i.d., three times a day.

References