CASE REPORT

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia: an unusual cause of cyclical ectopic adrenocorticotrophic syndrome

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ABSTRACT. We present the case of a 73-year-old woman who presented with clinical features of Cushing's syndrome, confirmed biochemically with elevated levels of cortisol and adrenocorticotrophic hormone (ACTH). Petrosal venous sampling showed no ACTH gradient and MRI of pituitary was normal, suggesting ectopic ACTH production. In the course of further investigations, a thoracic CT was carried out to look for evidence of bronchial neoplasm. Although there was no discrete tumour identified, CT revealed widespread fine nodularity in the right middle and lower lobe. Subsequent trans-bronchial and video-assisted thorascopic biopsy showed pulmonary tumourlets and two typical carcinoid tumours on a background of diffuse idiopathic pulmonary neuroendocrine cell neoplasia (DIPNECH). We describe the clinical, radiological and histological features of this rare condition.

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Approximately 15–20% of cases of Cushing's syndrome are caused by ectopic adrenocorticotrophic hormone (ACTH) secretion [1]. This is most often due to carcinoma of the lung. Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is an unusual disorder in which there is a nodular proliferation of airway neuroendocrine cells. It is a very rare but recognised cause of ectopic ACTH production. We report on a case of a 73-year-old woman who presented with cyclical Cushing's syndrome due to biopsy-proven DIPNECH.

Case report

A 73-year-old woman presented to her local hospital as an emergency with hypertension and tachycardia. She had a medical history of hypertension, for which she was taking slow release nifedipine (30 mg day⁻¹), but no other relevant clinical history. Clinical examination was essentially normal apart from moderate scalp hair thinning. Laboratory testing of her blood on admission showed severe hypokalaemia with a potassium level of 1.6 mmol l⁻¹ (normal range 3.5–5 mmol l⁻¹). She had no major features of cortisol excess and was not pigmented; however, serial midnight plasma cortisol measurements were found to be grossly elevated (measuring up to 1900 nmol l⁻¹; normal 50–290 nmol l⁻¹). These were not suppressed during administration of dexamethasone at

2 mg four times per day for 2 days. The patient's plasma levels of ACTH (0800 hours) were inappropriately raised for the level of cortisol at 27 mU l⁻¹ (normal range <20 mU l⁻¹). As these features were in keeping with either severe pituitary-dependent Cushing's disease or ectopic ACTH syndrome, the patient underwent MRI of the pituitary, which was normal, and CT of the thorax, which showed relatively widespread fine nodularity in the right middle and lower lobes but no features to suggest lung cancer (Figure 1).

As the patient's presentation was most in keeping with ectopic ACTH secretion, arrangement was made for further investigations to be carried out as an inpatient in a specialist centre. Her condition spontaneously improved without any definitive medical treatment; plasma and urinary cortisol levels 12 weeks after the initial presentation were within normal limits. However, urinary excretion of 5-hydroxyindoleacetic acid (5HIAA) was elevated at 61 µmol 24 h⁻¹ (normal range <50 µmol 24 h⁻¹), consistent with carcinoid syndrome, and it was felt that the patient may have a small bronchial carcinoid tumour that was intermittently secreting excess ACTH.

3 months later, the patient was admitted to hospital with flushing, proximal muscle weakness and hypokalaemia. She had clinical features of cortisol excess, including facial rounding and plethora, easy bruising and proximal myopathy. 24-h urinary excretion of cortisol was grossly elevated, and plasma levels of cortisol were raised, with clear loss of diurnal rhythm (midnight cortisol 638 nmol l⁻¹). Cortisol levels did not reduce following a dexamethasone suppression test, and ACTH levels were also consistently elevated. Petrosal sinus and peripheral venous sampling was performed but did not

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Figure 1. CT of the thorax with 5 mm reconstructions showing multiple small (<5 mm) nodules in the right middle and lower lobes.

identify a clear gradient of ACTH across any territory. Further imaging to identify a possible source of ACTH, including an ^{111}In -labelled octreotide scan and positron emission tomography (PET), was negative.

A repeat CT of the thorax showed persisting nodular abnormality in the right lung. The patient underwent bronchoscopy, which appeared normal although trans-bronchial biopsies showed widespread pulmonary neuroendocrine cell hyperplasia that, in the context of a diffuse process radiologically, was in keeping with DIPNECH. The patient subsequently had a video-assisted thoracoscopic surgery biopsy that showed pulmonary tumourlets and two typical carcinoid tumours

on a background of DIPNECH (Figure 2a). Immunohistochemical staining for ACTH showed patchy positivity in areas of neuroendocrine cell hyperplasia as well as within the carcinoid tumours and tumourlets (Figure 2b).

A presumed diagnosis was made of cyclical Cushing's syndrome due to ACTH excess caused by DIPNECH, tumourlets and carcinoid tumours. Although it was not possible to ascertain the exact contribution of each element, the widespread distribution of DIPNECH on the biopsy specimens suggested that this was the most significant process.

Owing to the diffuse radiological picture, primary surgical resection was not an option and the patient was initially managed medically using the somatostatin analogues metyrapone and octreotide. As is not uncommon in cases of ectopic ACTH secretion, these drugs failed to control fully the cortisol excess [2]. Because of the severity of her clinical features of hypercortisolism, bilateral adrenalectomy was performed to provide permanent cure. The patient remains well 5 years later, and continues on adrenal replacement therapy. A long-acting preparation of a somatostatin analogue (lanreotide) has been continued in an attempt to suppress progression of the pulmonary syndrome. Interval CT scans of the thorax show stable disease and ACTH levels remain elevated but have not progressed during this period. High-resolution CT (HRCT) of the lungs has also been performed and shows a diffuse mosaic pattern and air trapping — a characteristic feature of DIPNECH (Figure 3).

Discussion

A pulmonary tumourlet refers to a minute nodular proliferation of airway neuroendocrine cells that extend beyond the epithelium into the adjacent wall or lung parenchyma. The term DIPNECH describes a purely intraepithelial proliferation of the same cells. Tumourlets

(a)

(b)

Figure 2. (a) Section from the video-assisted thoracoscopic surgery biopsy showing a tumourlet (t) that is resulting in narrowing of the bronchiole lumen (arrows) (haematoxylin and eosin; magnification $\times 40$). (b) Immunohistochemical staining for adrenocorticotrophic hormone (ACTH) shows positive staining within an intraepithelial proliferation of neuroendocrine cells (arrows) in relation to a small airway (A) (anti-ACTH; magnification $\times 200$).

Figure 3. High-resolution CT at the level of the aortopulmonary window showing a mosaic pattern (a), which is accentuated on the expiratory study owing to air trapping (b).

range in size from minute microscopic foci to well-defined, grossly identifiable nodules measuring several millimetres in diameter. Nodules greater than 5 mm are generally considered to be small carcinoid tumours [3]. Pulmonary tumourlets and neuroendocrine cell hyperplasia are frequently associated with concomitant pulmonary disease such as bronchiectasis and parenchymal fibrosis. Our patient had evidence of DIPNECH, tumourlets and, by definition, carcinoid tumours, as two tumours were greater than 5 mm.

DIPNECH is a lung disease that is usually diagnosed in older women, but it has been observed in all age groups and both sexes [4]. Patients with this disorder are frequently asymptomatic and the syndrome is discovered incidentally; however, occasionally, it is discovered after a patient presents with a non-productive cough and dyspnoea. It is typically a fairly indolent and non-progressive disorder [5] and management is predominantly long-term close surveillance; the role of surgery is currently unclear [6]. Cushing's syndrome secondary to ectopic ACTH production is a very rare but recognised consequence of tumourlets/DIPNECH [7]; to the best of our knowledge, there are only five other case reports in the literature, and no previous reports of cyclical Cushing's syndrome in this circumstance. Cyclical Cushing's disease due to an ACTH-producing pituitary adenoma is well recognised; cyclical presentations due to ectopic ACTH production from carcinoid tumours have been described as very rare presentations [8], but not previously in the context of DIPNECH. The mechanism for the intermittent nature of the ACTH excess is unclear. However, it is evident from the case described that this can cause very severe cortisol excess, with a clinical presentation that resembles that seen in the ectopic syndromes associated with small cell primary lung tumours.

The most common HRCT findings are mosaicism and small nodules, although other features such as airway dilatation, bronchial wall thickening and atelectasis are recognised. CT can also be normal in the presence of DIPNECH [5]. Diffuse nodularity was the initial imaging finding in our patient, which correlates well with the pathological findings of multiple tumourlets and two typical carcinoids (Figure 1). This can create diagnostic difficulty, as the list of differential possibilities for pulmonary nodules is vast, and it has been suggested that pulmonary tumourlets should be considered in the differential diagnosis of small pulmonary nodules visible on CT [9]. Mosaicism is another common finding, and was the predominant abnormality on the subsequent expiratory HRCT performed on our patient. In healthy participants, small focal areas of low attenuation as well as small areas of air trapping can be seen. These most commonly affect the superior segments of the lower lobes and near the tip of the lingual [10], and usually involve less than 25% of the cross-sectional area of one lung at one scan level [11]. Mosaic attenuation and air trapping can be considered abnormal when they affect a volume of lung equal to or greater than a pulmonary segment and are not limited to the superior segment of the lower lobe or the tip of the lingula. Mosaic attenuation and air trapping is commonly seen on HRCT in patients who have obliterative bronchiolitis, regardless of aetiology. In obliterative bronchiolitis, peribronchiolar fibrosis causes narrowing of the airway lumen, which results in decreased ventilation of the lung distal to the narrowed airway. This causes reflex vasoconstriction and redistribution of blood flow to the uninvolved lung, resulting in a heterogeneous pattern of attenuation (mosaic attenuation) [10]. Similarly, the mosaic pattern seen in DIPNECH is thought to be caused by hypoventilation

of the alveoli distal to small airways that are obstructed or partially obstructed by aggregates of neuroendocrine cells (Figure 2a). This leads to secondary vasoconstriction with normal or increased perfusion in the uninvolved segments of lung [12]. The mosaic pattern is more conspicuous on expiratory studies owing to air trapping in the parts of the lung where there is narrowing of small airways (Figure 3). Several studies show that DIPNECH is typically indolent and non-progressive [4, 5], and our patient has not shown any significant progression on serial CTs carried out over a 5 year period.

In conclusion, DIPNECH/pulmonary tumourlets is a rare diagnosis. However, in patients with ectopic ACTH and no other obvious source, it should be considered. Although histopathology is required for the definitive diagnosis, HRCT can play an important role in the investigation of such patients. In the appropriate clinical context, the detection of pulmonary nodules and mosaicism with air trapping is highly suggestive of the diagnosis.

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