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Case Report

Ectopic Cushing Syndrome Secondary to Diffuse Idiopathic Neuroendocrine Cell Hyperplasia—A Report of 2 Cases

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Abstract

Ectopic ACTH secretion (EAS) accounts for 10% to 20% of all Cushing syndrome cases. Diffuse intrapulmonary neuroendocrine cell hyperplasia (DIPNECH), a poorly understood lung disease, is characterized by abnormal proliferation of neuroendocrine cells in the bronchial mucosa. It is thought to be a precursor of pulmonary carcinoid and has been associated with EAS in a handful of cases. We present 2 patients with clinical, radiological, and pathological features of DIPNECH who presented with florid Cushing syndrome secondary to EAS evidenced by rapid onset of symptoms, elevated plasma ACTH, and cortisol levels, and failed high-dose dexamethasone suppression testing. Treatment of hypercortisolism included excision of the involved lung and medical therapy with steroidogenesis inhibitors. Despite the aggressive initial management, hypercortisolism persisted. This case series highlights the importance of considering DIPNECH as a cause for Cushing syndrome in the appropriate clinical scenario and underscores the likelihood that surgery may not be curative because of the diffuse nature of this disease. Given the high mortality associated with EAS, prompt medical therapy, appropriate prophylaxis, and bilateral adrenalectomy can be lifesaving measures when initial surgery fails.

Key Words: ectopic Cushing syndrome, DIPNECH

Introduction

Diffuse idiopathic neuroendocrine cell hyperplasia (DIPNECH) is a rare, chronic, slowly progressive lung disease characterized by the abnormal proliferation of neuroendocrine cells in the bronchial mucosa, first described by Aguayo et al in 1992 (1). DIPNECH has since been increasingly reported in the literature, although prevalence data remain limited because of its rarity. Studies have suggested that DIPNECH may be a precursor to pulmonary carcinoid tumors, and, in rare circumstances, associated with hormone secretion. In exceedingly rare circumstances, DIPNECH is associated with ectopic ACTH production (2, 3). In most cases of ectopic ACTH secretion (EAS), the presentation is dramatic with rapidly worsening symptoms of hypokalemic metabolic alkalosis, insulin resistance, and disorientation. Here, we report 2 patients who presented with severe EAS thought to be secondary to DIPNECH.

Case Presentation

Case #1

A 37-year-old female initially presented with a 7-year history of intermittent, nonproductive cough. She had initially been diagnosed with asthma; however, her symptoms had persisted despite bronchodilator therapy. A chest computed tomography (CT) scan revealed innumerable small, well-circumscribed nodules scattered throughout the lungs without calcification or evidence of lymphadenopathy. Pulmonary function tests demonstrated a mild mixed ventilatory defect with severe air trapping. She underwent a left lung wedge biopsy that identified multiple carcinoid tumors and tumorlets without atypia, necrosis, or appreciable mitotic figures. Immunohistochemistry (IHC) was positive for AE-1/3, chromogranin, synaptophysin, and thyroid transcription factor-1. Therapy with monthly octreotide acetate injections was initiated with improvement in her symptoms. She was followed over the next 14 years, during which time her symptoms and pulmonary lesions remained stable.

About 15n years after her initial diagnosis, she presented with rapidly progressive dyspnea, weakness, lower extremity edema, skin darkening, easy bruising, increasing abdominal girth, facial swelling, and back pain in addition to recently diagnosed diabetes and hypertension.

Case #2

A 73-year-old female with a medical history of severe intellectual disability (nonverbal), blindness, and hypertension presented to the emergency department with several weeks of anasarca and weakness. Physical examination was notable for severe diffuse edema with supraclavicular fullness and facial hirsutism.

Diagnostic Assessment

Case #1

Initial laboratory tests were notable for hypokalemia and metabolic alkalosis. A chest CT scan revealed stable ground-glass opacities and innumerable subcentimeter nodules (Fig. 1). Magnetic resonance imaging (MRI) of the spine

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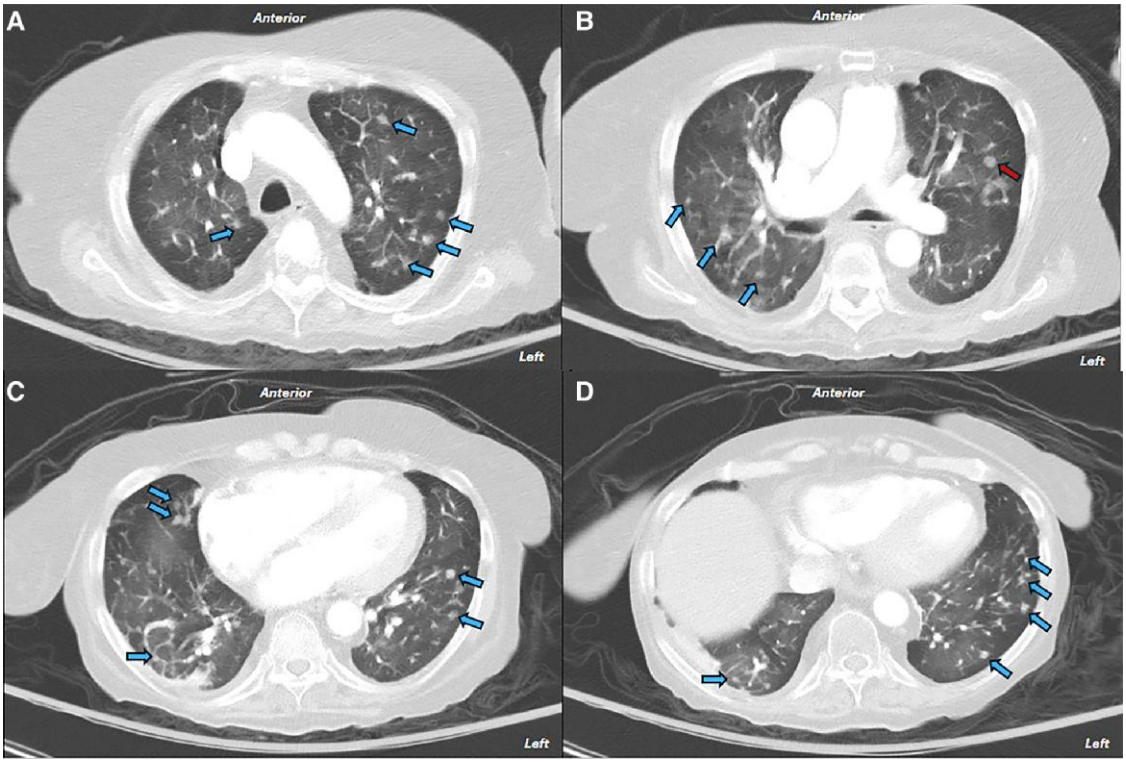

Figure 1. A CT scan of the chest with contrast from case #1 showing ground-glass opacities and numerous subcentimeter nodules. (A) Lung apex, (B) mid-thoracic segment, (C) mid-to-low lung bases, and (D) lower lung bases. Arrows shown in most lung field highlight some of the subcentimeter nodules, whereas in figure B left lung showed a larger nodule measuring nearly 6 mm.

Table 1. Additional laboratory data from cases 1 and 2

Test	Case 1	Case 2	Reference range
Cortisol	26.86 μg/dL; 741.0674 nmol/L[a]	50.1 μg/dL; 1382.259 nmol/L[a]	5 to 25 mcg/dL; 138 to 690 nmol/L
ACTH	229.0 pg/mL; 50.38 pmol/L[a]	Missing data	10 to 60 pg/mL; 1.3 to 16.7 pmol/L
24-hour urine cortisol	1776.8 mcg	1845.9 mcg	4.0 to 50.0 mcg/24 h
Late-night salivary cortisol	Missing data	1.72 mcg/dL; 47.4 nmol/L	<0.09 mcg/dL; <2.5 nmol/L
1 mg dexamethasone suppression test			
Cortisol	32.8 μg/dL; 904.95 nmol/L	26.3 μg/dL; 725.6 nmol/L	<1.8 μg/dL; <50 nmol/L
ACTH	317.0 pg/mL; 69.74 pmol/L	Missing data	
8-mg dexamethasone suppression test			
Cortisol	36.3 μg/dL; 1001.5 nmol/L	37.1 μg/dL; 1023. 6 nmol/L	<1.8 μg/dL; <50 nmol/L
ACTH	193.0 pg/mL; 42.46 pmol/L	209.0 pg/mL; 45.98 pmol/L	

[a]Random levels collected at nighttime.

revealed compression fractures of T5 and T6. Additional testing was performed and confirmed the presence of ACTH-mediated hypercortisolism (Table 1). MRI of the brain failed to locate a pituitary lesion. The rapidity of symptom onset, laboratory tests, and presence of lung lesions were highly suggestive of ectopic ACTH production most likely from known pulmonary carcinoid.

Case #2

Initial evaluation revealed hypokalemia, metabolic alkalosis, and hypertension. Further testing confirmed ACTH-mediated hypercortisolism (Table 1). Pituitary and sella MRI revealed no gross sellar or suprasellar mass. A CT scan of the neck, chest, abdomen, and pelvis revealed a 2.5-cm well-circumscribed right middle lobe pulmonary nodule, a 3-mm nodule in the right lower lobe, and

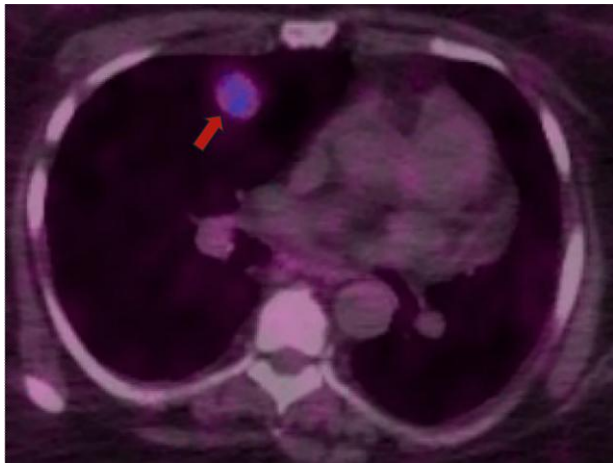

Figure 2. NM Gallium-68 PET/CT from case #2 showing a well-circumscribed 2.1-cm right middle lobe pulmonary nodule with mildly increased DOTATATE uptake.

mild thickening of the bilateral adrenal glands. A gallium-DOTATATE scan demonstrated a 2.1-cm right-middle lobe pulmonary nodule with mildly increased DOTATATE uptake (Fig. 2). A transbronchial biopsy of the right middle lobe nodule was performed confirming a carcinoid tumor with no mitosis or necrosis. IHC stained positive for chromogranin, synaptophysin, CD56, and AE1/3. Ki-67 stain showed a low proliferative index.

Treatment

Case #1

Ketoconazole and spironolactone were initiated for the treatment of hypercortisolism and hypokalemia, respectively. However, her hospital course was complicated by respiratory failure secondary to aspiration pneumonia and cardiac arrest necessitating intubation. Because of worsening metabolic derangements (hypernatremia, hypokalemia, hyperglycemia, and metabolic alkalosis), therapy was transitioned to etomidate with significant improvement, allowing for bilateral surgical adrenalectomy. Pathology revealed adrenal cortical hyperplasia.

Case #2

Ketoconazole was initiated and titrated with the goal to normalize 24-hour urine free cortisol levels. The patient subsequently underwent a right middle lobectomy, with pathology displaying 2 typical carcinoid tumors, 2.8 and 0.7 cm in greatest dimension, respectively. The report also noted multiple carcinoid tumorlets and foci of neuroendocrine cell hyperplasia raising concerns for DIPNECH. IHC staining for ACTH was positive in the 2.8- and 0.7-cm carcinoid tumors as well as 2 additional carcinoid tumorlets that were tested.

Outcome and Follow-up

Case #1

Postoperative complications resulted in persistent respiratory failure necessitating tracheostomy and percutaneous endoscopic gastrostomy tube placement. She was discharged to a long-term acute care hospital where she died 6 weeks later of an unknown cause.

Case #2

Four days following surgery, morning cortisol was 8.1 µg/dL and ACTH was 33.5 pg/mL. The patient was discharged with plans for close outpatient follow-up of cortisol levels. Four weeks after hospital discharge, she presented to the emergency department with recurrence of anasarca, lethargy, as well as profound hypokalemia and metabolic alkalosis. Spironolactone and ketoconazole were resumed. A chest CT scan revealed right middle lobectomy, a stable 4-mm nodule along the right major fissure, and nodularity in the right lung apex, similar to previous imaging. One week after admission, the patient suffered a cardiac arrest after an aspiration event. She was resuscitated and intubated but developed septic shock. The decision was ultimately made to transition her care to hospice.

Discussion

DIPNECH is a poorly understood pulmonary disorder that is an extremely rare cause of EAS (1-3). Identifying DIPNECH remains a challenge because of the absence of consensus radiologic, clinical, and pathologic diagnostic criteria (1). The World Health Organization has proposed defining DIPNECH by purely histologic criteria, describing it as a "generalized proliferation of scattered single cells, small nodules (neuroendocrine bodies) or linear proliferation of pulmonary neuroendocrine cells that may be confined to the bronchial and bronchiolar epithelium, include local extraluminal proliferation in the form of tumourlets (<5 mm), or extend to the development of carcinoid tumours (>5 mm)." The World Health Organization also considers DIPNECH to be a preinvasive lesion that may give rise to pulmonary carcinoid tumors. In addition to histologic findings, others have suggested considering other classic findings such as female sex, nonsmoking status, respiratory symptoms, airflow obstruction on pulmonary function tests, mosaic attenuation with air trapping on chest imaging, and constrictive obliterative bronchiolitis when determining the diagnosis (1). In our first case, the patient exhibited many typical DIPNECH features, leading to a likely diagnosis despite nonspecific lung biopsy findings. The second patient had some characteristic DIPNECH features, such as being a nonsmoking female with classic pathology but lacked typical respiratory symptoms and radiologic findings. This highlights the need to consider clinical, radiological, and histopathological findings when diagnosing DIPNECH. Treatment of nonhormone-secreting DIPNECH may involve somatostatin analogues (4), as used in our first patient effectively controlling her respiratory symptoms for more than a decade.

EAS is an uncommon entity that accounts for 10% to 20% of individuals with Cushing syndrome (5), and DIPNECH is 1 of its most rare causes. DIPNECH-associated EAS follows a similar disease course to other EAS causes, with rapid symptom onset and moderate to severe hypercortisolism. This leads to issues such as hypokalemic metabolic alkalosis and hypertension by saturating the enzyme that inactivates cortisol, allowing active cortisol to act on mineralocorticoid receptors (6). Other complications may include hypercoagulability, osteoporosis, impaired immune response, hyperglycemia, and peptic ulcer disease, all of which need to be monitored (7). Prophylaxis against these complications should be considered in special circumstances, particularly in the hospitalized patient and the perioperative period. Both patients presented

received thromboprophylaxis as well prophylaxis against *Pneumocystis jirovecii*.

Given its dramatic presentation and the high risk of mortality associated with untreated EAS (8), urgent control of hypercortisolism with surgical resection of the primary tumor is first-line therapy because it has a high chance of cure in nonmetastatic disease (9). Although undetectable ACTH and cortisol in the immediate postoperative period indicates cure, in a small percentage of patients, cure may not be immediately apparent (10). It is important to follow these patients over time with measurements of late-night salivary cortisol and 24-hour urine free cortisol to document cure or detect early recurrence. Patients cured of their disease should start glucocorticoid replacement and undergo serial adrenal axis testing over 6 to 12 months to assess adrenal recovery and gradually taper steroids. Recurrence in EAS, as seen in case 2, indicates metastatic disease (11) and requires considering the next line of therapy.

When surgery cannot cure hypercortisolism or must be delayed, medical therapy with steroidogenesis inhibitors (SI) or glucocorticoid receptor blocker, mifepristone, plays an invaluable role in managing symptoms. The choice of therapy depends on cost, availability, and patient factors. In the case of all medications, except mifepristone, the goal of therapy is to normalize cortisol levels. Ketoconazole was chosen for the management of hypercortisolism in our patients because of the ease of availability and rapid onset of action. Spironolactone was added to for its magnetic resonance blocking properties. We were unable to obtain metyrapone because of insurance coverage issues and limited availability in the region. Although etomidate was used in our first patient, it was not permitted for use by the intensive care unit pharmacy in our second patient because of fair control with ketoconazole, despite studies that have reported clear benefit from its use (12). This highlights the complexity associated with managing EAS even in large academic centers. Osilodrostat and levoketoconazole are available and effective SIs that could have been considered had ketoconazole failed or long-term medical therapy contemplated. Some experts have suggested the effectiveness of combination therapies such as etomidate and osilodrostat (13) or mitotane, metyrapone, and ketoconazole (14) in severe disease. Others suggest a "block and replace" strategy using SIs with physiologic glucocorticoid replacement to prevent adrenal insufficiency by suppressing endogenous steroid production (11). When all else fails, bilateral adrenalectomy is a life-saving measure for rapidly curing hypercortisolism (11).

In conclusion, EAS has high mortality and requires urgent treatment to minimize complications. DIPNECH is rare, poorly characterized, and rarely linked to ECS. Its diffuse nature makes it less responsive to surgery, often necessitating medical management or bilateral adrenalectomy.

Learning Points

- DIPNECH is a rare pulmonary disorder characterized by diffuse proliferation of pulmonary neuroendocrine cells, and its diagnosis can be challenging because of nonspecific symptoms.
- Ectopic ACTH production should be considered in patients with DIPNECH presenting with Cushing syndrome features.
- The management of EAS can include surgical excision of the primary tumor, medical therapy, and bilateral adrenalectomy.

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Contributors

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Disclosures

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Informed Patient Consent for Publication

Signed informed consent could not be obtained from the patients or proxies but has been approved by the treating institution.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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