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Chromogranin-A Levels and Refractory Bronchospasm in Interstitial Lung Disease: A Preliminary Report on the Favourable Response to Octreotide

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Authors' contributions

This work was carried out in collaboration between all authors. Authors NW and OE designed the study and wrote the protocol. Authors NW, OE and BJ managed both patients and wrote the manuscript. Author MAB managed the patient in the ICU and author SH carried out the nuclear medicine scans. Author BAR did the literature searches. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Aims: A wide variety of lung pathologies are associated with pulmonary neuroendocrine cell hyperplasia (PNECH).
Presentation of Case: We report two patients with interstitial lung disease (ILD), severe persistent bronchospasm not responding to conventional therapy, and raised chromogranin-A (Cg-A) levels. A neuroendocrine tumour (NET) was suspected and both were given a therapeutic trial of octreotide. This led not only to a dramatic clinical improvement but also to the normalization of Cg-A levels. Cg-A levels were elevated in 6 additional patients with interstitial involvement but without bronchospasm. The raised Cg-A levels in these 8 patients and the response to octreotide in two

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who had bronchospasm supports a diagnosis of PNECH in ILD.
Conclusion: Cg-A levels should be measured in all patients with ILD. An octreotide trial should be considered in symptomatic patients with interstitial lung disease and elevated chromogranin levels.

Keywords: Chromogranin-A; interstitial lung disease; octreotide.

1. INTRODUCTION

Pulmonary neuroendocrine cells (PNEC's) are distributed throughout the lung [1]. They store and secrete a wide variety of various amines, peptides and chromogranin-A (Cg-A) [2,3]. Hyperplasia of the PNEC's may be primary or reactive. The primary form, diffuse idiopathic PNEC hyperplasia (DIPNECH), is apparently rare [4,5] and diagnosis requires a lung biopsy. These cells have somatostatin receptors which will respond to the long acting somatostatin analogue, octreotide. The use of octreotide will inhibit the secretory products of PNEC. Patients with DIPNECH with disease progression who received somatostatin (SS) analogues showed improvement in pulmonary function with a significant reduction of their Cg-A levels [5]. Reactive pulmonary neuroendocrine cell hyperplasia (PNECH) is seen in cigarette smokers, persons living at high altitudes and patients with bronchiectasis, cystic fibrosis, tuberculosis and pulmonary fibrosis [4,6]. Cg-A levels are increased in smokers with airway obstruction [7] but levels in the other disorders have not been studied.

We report a dramatic effect of octreotide in reversing severe refractory bronchospasm in two patients with interstitial lung disease (ILD). Furthermore, we found chromogranin-A (Cg-A) levels to be raised in patients with ILD of different aetiologies indicating that reactive PNECH may be much more common than previously realized and therefore potentially amenable to treatment with somatostatin (SS) analogues.

2. CASE REPORT

2.1 Case 1

A 70-year-old female, having asthma, moderately severe obstructive sleep apnoea and idiopathic pulmonary fibrosis (IPF) was admitted with severe bronchospasm and a low haemoglobin of 8.5gm%. Her asthma was partly controlled with budesonide and formoterol combination inhaler and monteleukast tablets. The diagnosis of IPF was based on clinico-radiological features. High resolution computed tomography (HRCT) was showing minimal sub pleural cystic changes, interstitial thickening and minimal ground glass opacities suggesting a usual interstitial pneumonia (UIP) pattern (Figs. 1A and B). A lung biopsy was not done at the time of diagnosis as she was not keen on surgery and had only minimal symptoms.

She was not on any specific treatment. Lately she was using home oxygen. CT abdomen, done as a part of the work up for the recent drop in haemoglobin, revealed an elongated mass 10 x 4 cm between the caecum and the right ovary raising the possibility of a mucocele of the appendix or a carcinoid tumour. The patient's serum Cg-A was 748 Ug/L (Normal range 22 – 97Ug/L, ELISA, Dako, Denmark) showing a substantial elevation. But the urinary 5-hydroxy indole acetic acid (5-HIAA) level was normal, 31U/ml. The indium-111-octreotide (^{111}In-octreotide) scan was negative. She was discharged on her regular medications, home oxygen and non-invasive ventilation (NIV) in the night.

She was readmitted shortly afterwards with increasing shortness of breath. Her serum creatinine level was normal. In view of the persistent bronchospasm while taking monteleukast tablets, budesonide and formoterol inhalers together with the finding of an elevated Cg-A levels, she was given a therapeutic trial of octreotide 100mcg subcutaneously every 8 hours for 7 days. She showed rapid clinical and biochemical improvements (Fig. 2A). Her wheezing improved and she was able to maintain an O_2 saturation of 97 – 99% on room air by the fourth day. A right hemi colectomy was successfully carried out. Histopathological examination did not reveal any evidence for carcinoid tumour but showed features of low-grade mucinous adenocarcinoma. A few days later wheezing recurred and the Cg-A level increased. Octreotide LA 20 mg, every three weeks, was started and continued for three months. She remained relatively well with minimal wheezing, normal Cg-A levels (Fig. 2B) and was off oxygen for most of the time.

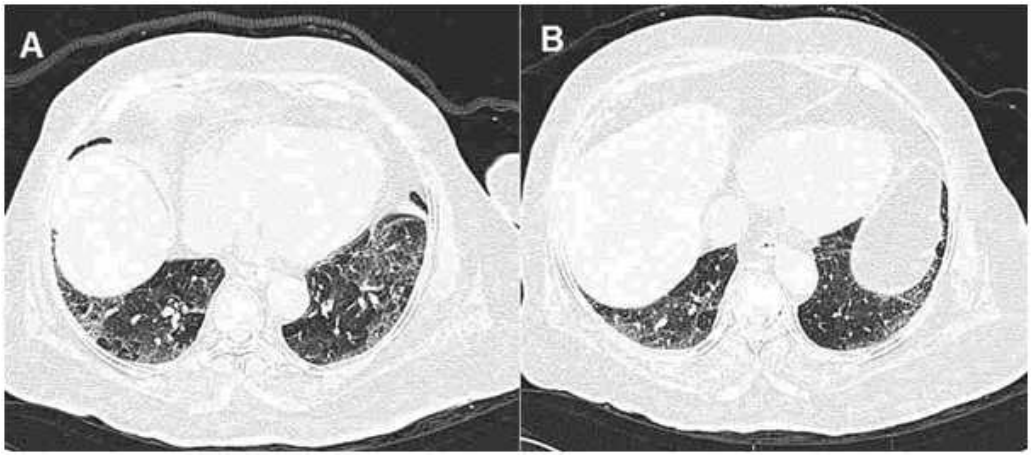

Fig. 1. High resolution computed tomography (HRCT) showing minimal sub pleural cystic changes, interstitial thickening and some ground glass opacities

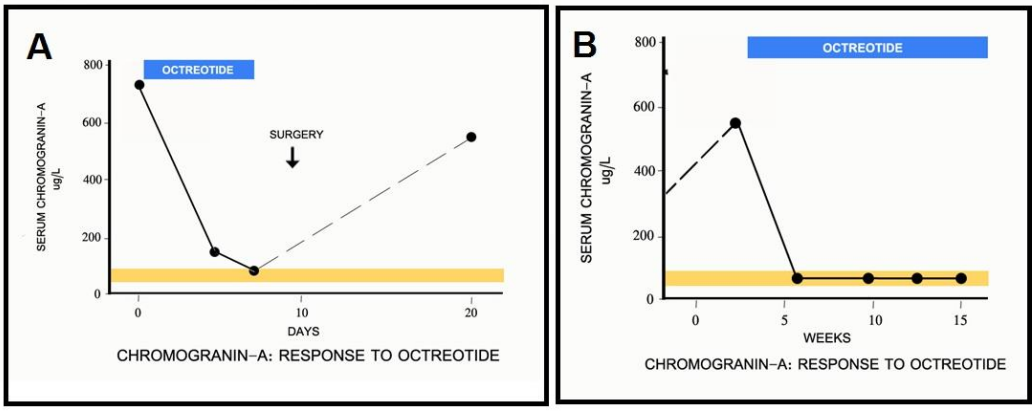

Fig. 2. Chromogranin-A levels in patient 1 showing the response to octreotide. (A) Acute over 7 days, (B) Long term over 12 weeks

2.2 Case 2

A 36 year old man with a history of asthma taking only salbutamol on demand was admitted to the intensive care unit with illicit drug overdose, acute renal and liver injury. He was in respiratory distress and oxygen saturation was 80%. Auscultation of the chest revealed extensive polyphonic wheezes and crackles bilaterally. He received supportive care, dialysis, nebulized bronchodilators, intravenous steroids, intravenous magnesium sulphate and non-invasive ventilatory support. The response to treatment was poor and intubation with mechanical ventilation was initiated. His arterial blood showed combined respiratory and metabolic acidosis- pH 7.02, PCO2-79 mmHg, HCO3- 17 mmol/L, SaO2- 99% while on NIV with 80% oxygen.

After intubation, he continued to have bronchospasm and required high peak inspiratory pressures to maintain a target tidal volume of 6ml per kg ideal body weight. He was given intravenous ketamine and aminophylline as additional bronchodilators. However, he continued to have severe wheeze and could not be weaned from mechanical ventilation. Attempts at extubation failed twice and was reintubated on the same day each time. His course was complicated by episodic severe bronchospasm leading even to silent chest at some points and frequent drop in tidal volume on pressure control ventilation. This led to barotrauma and he developed pneumothoraces bilaterally for which intercostal drains were inserted. A month after admission a tracheotomy was done but he still needed ventilatory assistance most of the time. HRCT showed interstitial thickening and a few

areas of traction bronchiectasis mainly in the upper zone with some emphysematous changes. (Figs. 3A & B).

Due to his bad outcome, serum Cg-A was measured. Although the ^{111}In-octreotide scan was negative, he was given octreotide 100mcg subcutaneously every eight hours as a therapeutic trial since the Cg-A level was high, >400 U/L (Normal 0-22 U/L, ELISA, Cisbio Bioassays, France). The serum creatinine level was in the normal range when the Cg-A was measured. There were no more episodes of bronchospasm after the initial treatment. He was weaned off mechanical ventilation in 5 days and was discharged from the intensive care with oxygen. He remained in the hospital for a few weeks more and was finally discharged after a successful closure of the tracheostomy. Cg-A response to the treatment is shown in Fig. 4.

We also measured Cg-A levels in 6 additional patients with interstitial lung disease. Cg-A levels were elevated in all these patients and they did not have evidence for bronchospasm (Table 1)

3. DISCUSSION

These two patients with interstitial lung involvement and severe bronchospasm, refractory to conventional treatment, recovered rapidly when given octreotide. This is unlikely to have been a coincidence, as their improvement coincided with a fall and normalization of the initially elevated serum Cg-A levels. Furthermore, withholding octreotide after surgery (Patient 1) coincided with increased wheezing, a rising Cg-A, and a fall in oxygen saturation which corrected as soon as the treatment was restarted. Moreover, Cg-A levels were elevated in a few other patients with interstitial lung involvement.

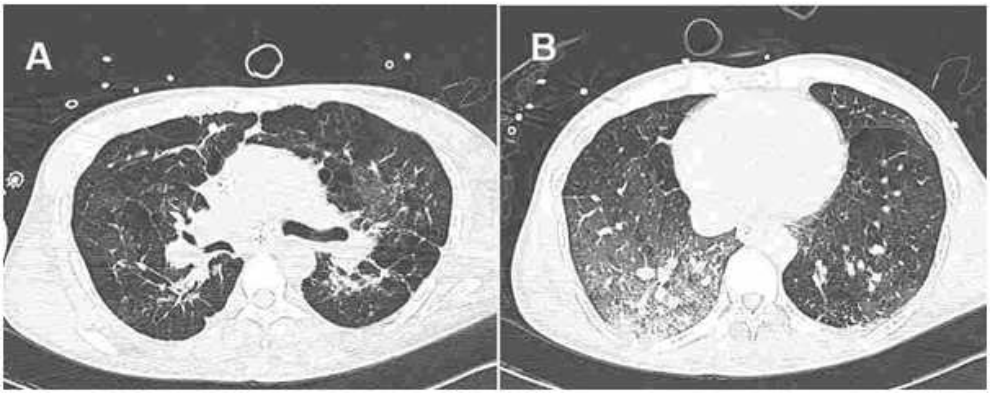

Fig. 3. HRCT showing interstitial thickening and a few areas of traction bronchiectasis mainly in the upper zone with some emphysematous changes

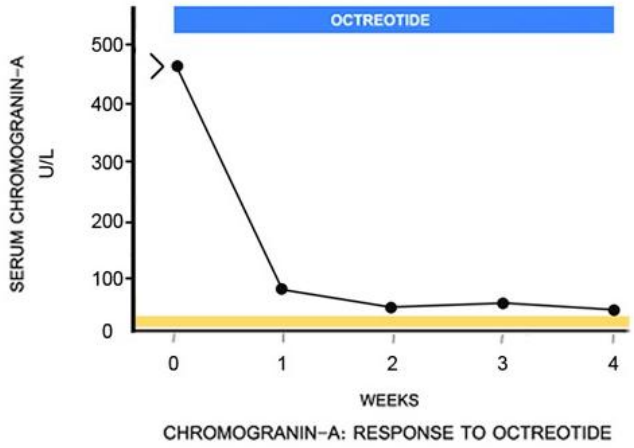

Fig. 4. Chromogranin-A levels in patient 2 showing the response to octreotide

Table 1. Chromogranin-A levels in patients with different forms of interstitial lung involvement

Patients	Age	Sex	Diagnosis	Cg-A (U/L) (Normal 0-22)
Reported patients				
1	75	F	Idiopathic pulmonary fibrosis, asthma	748*
2	36	M	Interstitial lung disease, asthma	400
Additional cases				
3	56	F	Rheumatoid arthritis, interstitial lung disease	128
4	60	F	Idiopathic pulmonary fibrosis	131
5	36	F	Systemic lupus, Interstitial lung disease	174
6	61	M	Sarcoidosis, stage III	53
7	54	F	Idiopathic pulmonary fibrosis	62
8	63	F	Idiopathic pulmonary fibrosis	208

**Normal range for this particular test using another test kit- 27-94 Ug/L*

Initially, we suspected that these two patients had a neuroendocrine tumour (NET) responsible for the bronchospasm but the negative octreotide scans and the finding of elevated Cg-A levels in other patients with ILD makes this diagnosis of PNECH highly likely. Patient 1 has all the features of DIPNECH being female with late onset dyspnoea and wheezing but this diagnosis requires a lung biopsy which was not obtained. This disorder is considered to be preinvasive [8] and may give rise to the development of small tumourlets <5 mm or pulmonary neuroendocrine tumours (PNETs) if >5 mm in diameter [9]. These lesions may be multiple and have on rare occasions been documented to cause ACTH dependant Cushing's disease [10]. Another patient labelled as having asthma was found to have reactive DNECH of uncertain cause during post-mortem studies [11]. The finding of elevated Cg-A levels in patients with ILD of different aetiologies indicates that PNECH whether idiopathic primary or reactive might benefit with treatment with SS analogues. Somewhat surprisingly Cg-A levels have not been routinely measured in patients with PNECH of any cause although lung fibroblasts have been demonstrated to express predominantly SS 2 receptors [12] and patients with IPF have increased lung uptake of ^{111}In-octreotide [13]. Interestingly, the same authors have data suggesting that long term treatment with octreotide will delay disease progression in such patients [14]. However, ^{111}In-octreotide cannot detect tumours less than 1 cm in diameter and more sensitive compounds are needed to identify tumourlets [15]. This may explain the negative scans in our patients. However, Cg-A level were not reported before or during treatment in any of these studies. Gorshtein et al. [5] reviewing data from 100 patients with DIPNECH found that Cg-A levels was measured in only 11 cases though all had multiple tumorlets. Moreover, he noticed that the treatment with octreotide was associated with an improvement in pulmonary function and a fall in the Cg-A in all the 6 patients who had raised levels.

Based on the above observations, we are now measuring Cg-A levels in all our patients with ILD with an intention to offer octreotide in select cases.

4. CONCLUSION

Patients with interstitial lung disease and raised Cg-A levels are likely to have PNECH. Symptomatic PNECH patients might respond to treatment with octreotide. Cg-A levels should be measured in all patients with Interstitial lung disease and late onset wheezing to exclude PNECH.

CONSENT

Written informed consents have been taken for publication of the submitted article and accompanying images from the patient's grandson in the first and the patient himself in the second case.

ETHICAL APPROVAL

Consent for the use of octreotide in the first patient was obtained from her son who is a medical doctor. Second patient was initially treated without consent as he was on a ventilator and no family members were available. After extubation he consented to continue on octreotide.

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We would like to thank both the patients for consenting to our treatment.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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