64. His treatment at home consisted of continuous O2 delivered by an oxygen concentrator, sambines, corticosteroids and bronchodilators.

His major complaint was persistent dyspnea in the sitting position that improved in the prone position. Physical examination revealed reduced bilateral breath sounds, malleolar edema and digital clubbing.

The chest x-ray film showed limited right apical calcified micronodular infiltration and enlarged pulmonary arteries. Lung function at rest, arterial blood gas levels and heart hemodynamics are presented in Tables 1 and 2. These results show increased hypoxemia in the sitting position without changes in PaCO2. Cardiac output was slightly increased in the prone position without significant changes in FAP, PW and CVO2. Oxygen consumption (Vo2) was found to be higher in the prone than in the sitting position. The SaO2 measured by ear oximeter showed a mean of 82% in the sitting position and of 87% in the prone position. A right-left intracardiac shunt was excluded through echocardiographic examination. Rib cage motion, abdominal motion (registered by magnetometers) and the sum of both signals (total ventilation) was almost identical in the two positions (Table 3).

Distribution of lung perfusion and ventilation was investigated, using respectively 19mTcMAA and inhalation of 82Kr, in both the sitting and prone positions. The sitting position had a deleterious effect on the V/Q ratio (Fig 1). Indeed, in this position, the pulmonary perfusion was predominant in the lung bases. In the prone position, the perfusion was also distributed to the top and was more matched with ventilation. Thus, the V/Q ratio was clearly more homogeneous in the prone than in the sitting position.

One month later, the V/Q ratio was measured 80 minutes after oral ingestion of 100 mg almitrine bisemisil. This treatment improved the V/Q ratio dramatically in the sitting position. Although regional ventilation changed slightly, perfusion was more directed to the top, leading to better matching of perfusion to ventilation. The patient stopped this treatment because of abdominal pain (Fig 1).

Three months later, the control of isotopic V/Q ratio showed similar results as in the control (Fig 1). The patient died three months after this last investigation and result of a macroscopic anatomic examination excluded an arteriovenous malformation either in the basal lungs or in the heart.

**DISCUSSION**

Our patient experienced severe "platypnea"; this has already been described by Altman and Robin" in one patient with severe COPD. The patient described is rather unique since in the upright position, FAP and ventilation increased while systemic blood pressure decreased (suggesting low cardiac output). The authors postulated pulmonary and vascular compressions due to high alveolar pressure (diffuse zone 1 phenomenon). Such dramatic changes, especially in pulmonary pressure and cardiac output, were not observed in our patient.

In COPD patients, the effect of recumbent vs upright positions has been studied. It appears that the supine position induces, in all subjects, a lowering of FRC, an increase in cardiac output and in venous content in O2. The changes in PaO2 depends upon the capacity to maintain ventilation. A decrease in ventilation will lead to a decrease in PaO2 and increase in PCO2; while on the contrary, a decrease in the respiratory drive may result in an increase in PaO2 and decrease in PCO2. Our patient probably behaves as the latter group, but changes in PaO2 are surprisingly high as compared to a mean increase of 4.3 mm Hg in the recumbent position in the study of Minh et al. Furthermore, venous content in O2 remains unchanged (Table 1). Thus, we feel that the V/Q changes in our patient may not be explained exclusively by either a zone 1 phenomenon or by the observed changes in cardiac output and the expected changes in ventilation. The larger Vo2 observed in the prone position than in sitting is difficult to explain since ventilation was identical in both positions. However, the type of breathing was different and one may speculate that the probable greater use of the diaphragm, suggested by the greater abdominal displacement in the prone position, could have increased Vo2.

The ventilation/perfusion studies performed in our patient showed that the sitting position induced a significant shift of perfusion (by gravitational effect) to the lung bases which remained poorly ventilated, thus inducing topographic areas of low V/Q ratio. In COPD patients as in normal subjects, although the exact mechanism is not completely understood, it is hypothesized that hypoxic vascular constriction on a regional level may at least partially prevent such dramatic changes in V/Q. Therapy with almitrine, which has proven to potentiate the mechanism of pulmonary hypoxic vasoconstriction in patients with intact carotid bodies, produced dramatic changes in our patient in distribution of V/Q with better matching of ventilation and perfusion, especially at the lung bases.

In conclusion, the platypnea in our patient is probably related to severe hypoxia resulting from poor matching of the regional V/Q ratio, probably related to a poor vascular adaptive mechanism to regional hypoxia. This defect was partially corrected after ingestion of almitrine.

**REFERENCES**

4 Altman M, Robin ED. Platypnea (diffuse zone 1 phenomenon?). N Engl J Med 1969; 281:1347-48

**Episodic Ectopic ACTH Syndrome Associated with Pulmonary Infarctions**

Mario Sparagana, M.D.

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Episodic Ectopic ACTH Syndrome (Mario Sparagana)
The etiology of the ectopic ACTH syndrome, associated with certain tumors, is uncertain. The ectopic ACTH syndrome was diagnosed in our patient by the characteristic clinical and laboratory findings. Shortly after admission, pulmonary infarctions were documented by lung scans and computed tomography. After treatment with anticoagulants, his plasma ACTH level and its suppressibility became normal. There was no evidence of a tumor. The ectopic ACTH syndrome recurred one year later in conjunction with another episode of pulmonary infarctions. During anticoagulant therapy his infarctions cleared and his plasma ACTH level normalized. In the five years since the onset, no tumor has been found, and plasma ACTH level remains normal and suppressible. We propose that our patient's pulmonary infarctions stimulated pulmonary ACTH production, leading to Cushing's syndrome.

The ectopic ACTH syndrome is characterized by the production of corticotropin from a nonpituitary source, which then leads to Cushing's syndrome. Initially, the ectopic production of corticotropin was felt to be confined to neoplasms and somehow related to tumor biology. However, when assays became more sensitive, ACTH was demonstrated in normal human and rat tissues. The first case report of a patient with the ectopic ACTH syndrome, arising from inflammatory rather than neoplastic tissue, appeared in 1964.

In this report, we describe a similar patient who developed the typical ectopic ACTH syndrome, which appeared and disappeared in concert with two episodes of pulmonary infarctions, and who shows no evidence of a tumor after five years of close follow-up.

Table 1—Serial Studies of a Patient with Episodic Ectopic ACTH Syndrome Due to Pulmonary Infarctions

<table>
<thead>
<tr>
<th>Date</th>
<th>ACTH (pg/ml)</th>
<th>Cortisol (ng/ml)</th>
<th>K (mEq/L)</th>
<th>Glucose (mg/dl)</th>
<th>HCO₃⁻ (mEq/L)</th>
<th>Urine (mg/24 hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cortisol</td>
</tr>
<tr>
<td>8/82</td>
<td>500</td>
<td>430</td>
<td>2.0</td>
<td>252</td>
<td>41.9</td>
<td>0.245</td>
</tr>
<tr>
<td>9/30/82</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10/18/82</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.049</td>
</tr>
<tr>
<td>11/9/82</td>
<td>Anticoagulant therapy started</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/3/83</td>
<td>74</td>
<td>127</td>
<td></td>
<td></td>
<td></td>
<td>12.749</td>
</tr>
<tr>
<td>3/9/83</td>
<td>62</td>
<td>122</td>
<td></td>
<td></td>
<td></td>
<td>9.893</td>
</tr>
<tr>
<td>8/6/83</td>
<td>90</td>
<td>60</td>
<td></td>
<td></td>
<td></td>
<td>8.625</td>
</tr>
<tr>
<td>11/7/83</td>
<td>85</td>
<td>78</td>
<td>3.5</td>
<td>185</td>
<td></td>
<td>12/23/83</td>
</tr>
<tr>
<td>12/6/83</td>
<td>350</td>
<td>671</td>
<td>2.7</td>
<td>549</td>
<td>39</td>
<td>12/12/83</td>
</tr>
<tr>
<td>12/12/83</td>
<td>490</td>
<td>789</td>
<td>4.7</td>
<td>154</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12/23/83</td>
<td>Second ACTH gradient study (see Table 2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12/27/83</td>
</tr>
<tr>
<td>1/19/84</td>
<td>256</td>
<td>444</td>
<td>4.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/23/84</td>
<td>78</td>
<td>115</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/26-3/13/84</td>
<td>77-107</td>
<td>86-167</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4/13/84</td>
<td>78</td>
<td>136</td>
<td>4.3</td>
<td>99</td>
<td>27</td>
<td>5/8/84</td>
</tr>
<tr>
<td>4/20/84</td>
<td>Bilateral adrenalectomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10/30/84</td>
</tr>
<tr>
<td>5/9/84</td>
<td>241*</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td>11/84</td>
</tr>
<tr>
<td>8/27/85</td>
<td>106</td>
<td>49</td>
<td>4.0</td>
<td>82</td>
<td></td>
<td>8/27/85</td>
</tr>
<tr>
<td>6/4/86</td>
<td>299*</td>
<td>14</td>
<td>4.1</td>
<td>82</td>
<td>24.6</td>
<td>6/18/86</td>
</tr>
<tr>
<td>1/6/87</td>
<td>125</td>
<td>141</td>
<td>4.2</td>
<td>81</td>
<td>28.9</td>
<td>4/21/87</td>
</tr>
<tr>
<td>Normal</td>
<td>&lt;100</td>
<td>70-250</td>
<td>3.5-5.0</td>
<td>65-110</td>
<td>24-32</td>
<td></td>
</tr>
</tbody>
</table>

*Blood was drawn before the morning dose of cortisone was taken. Since 1/23/84, the plasma ACTH has always suppressed to less than 50 pg/ml when dexamethasone was administered orally.
Table 2—ACTH Gradient Study During the Second Episode of the Ectopic ACTH Syndrome

<table>
<thead>
<tr>
<th>Venous Sampling Site</th>
<th>ACTH (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inferior vena cava (below renal)</td>
<td>258</td>
</tr>
<tr>
<td>Left renal</td>
<td>179</td>
</tr>
<tr>
<td>Right renal</td>
<td>192</td>
</tr>
<tr>
<td>Left adrenal</td>
<td>203</td>
</tr>
<tr>
<td>Right adrenal</td>
<td>191</td>
</tr>
<tr>
<td>Inferior vena cava (above renal)</td>
<td>216</td>
</tr>
<tr>
<td>Hepatic vein</td>
<td>207</td>
</tr>
<tr>
<td>Left innominate</td>
<td>229</td>
</tr>
<tr>
<td>Right innominate</td>
<td>231</td>
</tr>
<tr>
<td>Left subclavian</td>
<td>229</td>
</tr>
<tr>
<td>Right subclavian</td>
<td>218</td>
</tr>
<tr>
<td>Left internal jugular</td>
<td>219</td>
</tr>
<tr>
<td>Right internal jugular</td>
<td>238</td>
</tr>
</tbody>
</table>

Discussion

The ectopic ACTH syndrome was first described in 1928. However, the nature of the association was not recognized until 1962, when an ACTH-like substance was extracted from the lung tumor of a patient with Cushing's syndrome. This was considered to be uncommon until 1974, when it was demonstrated that 14 of 15 patients with lung tumors had excessive quantities of immunoreactive "big" ACTH in their tumors and plasma. The "big" ACTH could be cleaved by trypsin or HCl to yield the smaller biologically active ACTH. These studies were later confirmed by Odell et al.

It later became apparent that certain nonpituitary tissues normally contain small amounts of hormones and fetal antigens, suggesting that the production of these substances might not be ectopic. It was suggested that any process which leads to an increased turnover of certain epithelial cells, where hormones and fetal antigens are made, might increase their concentration. Ulcerative colitis and pancreatitis, may lead to an elevation in carinoembryonic antigen similar to that seen with gastrointestinal neoplasms. Increased levels of alpha fetoprotein are seen with the regeneration of normal liver. Certain pulmonary inflammations are associated with an increase in plasma antidiuretic hormone, which may subside if the inflammation improves. Elevated pulmonary and plasma levels of immunoreactive "big" ACTH have been noted in patients with chronic obstructive lung disease.

The hormone peptides produced by neoplastic or inflamed tissue are usually large precursor molecules, and the unique clinical syndromes of hormone excess appear only if these are cleaved to the smaller, biologically active moieties. Many lung tumors produce pro-opiomelanocortin, although the ectopic ACTH syndrome is associated predominantly with small cell carcinoma of the lung because it can produce the smaller biologically active ACTH.

In 1984, the first case of the ectopic ACTH syndrome, caused by inflammatory lung tissue, was reported. Following the removal of a lung abscess, the patient's plasma ACTH level, and its suppressibility with corticosteroids, returned to normal. The abscess was shown by immunoperoxidase staining to contain ACTH, but no tumor cells were present. Our patient appears to be similar since he twice developed the ectopic ACTH syndrome in conjunction with pulmonary infarctions, and both pathologic conditions resolved during anticoagulant therapy. Five years after his initial presentation, there was no evidence of a tumorous source of ACTH.

Occasionally, a benign neoplasm, such as a bronchial carcinoid, produces the ectopic ACTH syndrome and the tumor may remain occult for years. However, in such cases, the plasma ACTH level remains continuously elevated. The corticotropic level in our patient rose and fell in concert with the clinical course of his pulmonary emboli. The stress associated with inflammations can give rise to elevated nonsuppressible plasma ACTH and cortisol levels. However, infections should not produce the florid features manifested by our patient.

We propose that the episodic ectopic ACTH syndrome in our patient was caused by ACTH secreted by his pulmonary infarctions. It was not feasible to prove this by direct demonstration of increased ACTH in the affected lung. However, we feel that the evidence presented is reasonably compelling.

References

6. Gerwitz G, Yalow RS. Ectopic ACTH production in carcinoma of

*Figure 1. Computed axial tomography scan of the patient's lung showing two pleural-based densities. The characteristic location, appearance and the presence of air bronchograms extending throughout these defects point to a diagnosis of multiple pulmonary infarctions.*

Episodic Ectopic ACTH Syndrome (Mario Sparagane)
Diet-Induced Changes in Trough Theophylline Concentrations in an Elderly Asthmatic Patient*

David Juan M.D.; Sang-Goo Shin M.D.; Thomas Holmes M.D.; and Richard L. Hughes M.D., F.C.C.P.

A 66-year-old obese man with asthma was given a hypocaloric (1100 Kcal) and low protein (35 g) diet for nine days. While receiving theophylline (Theodur), 200 mg bid, his morning trough theophylline concentrations rose from 3.40 μg/ml to 12.7 μg/ml by day 9 of this diet. Following discontinuation, his theophylline concentration fell to 5.95 μg/ml by day 6 on home diet. The patient lost 3.67 kg during the nine-day study. Thus, a brief exposure to a hypocaloric, low protein diet in this elderly patient with asthma caused a dramatic rise in trough theophylline concentrations.

Age, diet, smoking habits, concurrent medications, and disease states account for the wide intersubject variability in theophylline clearance. Protein-calorie malnutrition is a common problem among patients with chronic lung disease. In this report, a brief exposure to a hypocaloric, low protein diet in an elderly patient with asthma produced a significant increase in trough theophylline concentrations.

*From the Clinical Research Center, Northwestern Memorial Hospital, Clinical Pharmacology Center and Department of Medicine, Northwestern University Medical School, Chicago. This work was supported in part by Grant RR-00048 from the Division of Research Resources, National Institutes of Health, Department of Medicine Intramural Geriatric Grant and Vitalograph, Inc.

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Case Report

The patient was a 66-year-old, obese black man with chronic asthma. His usual medications included theophylline (Theodur), 200 mg twice a day (9 A.M., 4:30 P.M.); beclomethasone and metaproterenol inhalers; allopurinol, 300 mg; hydrochlorothiazide, 50 mg; and clonidine, 0.3 mg twice a day. He did not drink alcohol or smoke. The patient's initial weight was 128.1 kg (ideal body weight, 78 kg). On examination, there was no audible wheezing. His baseline arterial blood gas values were Po2, 75 mm Hg; Pco2, 40 mm Hg; and pH, 7.42. Baseline pulmonary function test results included FVC, 3.07 L (89 percent); FEV1, 2.03 L (73 percent); FEF25-75, 1.14 L/s (41 percent). The improvement after bronchodilator inhalation was FVC, 12 percent; FEV1, 21 percent; and FEF25-75, 43 percent. His usual home diet consisted of 2,800 Kcal and 196 g of protein a day. The test diet used in this study was based on a survey of elderly hospitalized patients and consisted of 1,100 Kcal, 35 g protein, 65 percent carbohydrate, and 22 percent fat for nine days. The patient ate all his meals in the Clinical Research Center under direct observation for the entire period as an outpatient.

The changes in trough (8 A.M.) theophylline concentrations and body weight in this patient during and after the test diet are shown in Figure 1. The prediet trough theophylline concentrations rose 300 percent while the patient lost 3.67 kg during the nine-day test diet. On home diet for six days, the trough theophylline level fell to 5.95 μg/ml. During the test diet, the patient reported less coughing and could breathe better.

Discussion

Theophylline is primarily eliminated by the hepatic cytochrome P450 enzyme system which can be modulated...

![Figure 1. Effects of a low calorie, low protein diet and home diet on body weight and trough theophylline concentration in the elderly asthmatic patient.](image-url)