Multiple Bronchial Adenomas, Cushing’s Syndrome and Hypokalemic Alkalosis
Report of a Case

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Three types of intrathoracic tumors, namely bronchogenic carcinomas⁴ (particularly the oat-cell type), thymomas,⁴ and bronchial adenomas⁵ are known to occur in association with adrenocortical hyperfunction. Only two cases of solitary bronchial adenoma associated with Cushing’s syndrome have been reported.⁶ The benign nature of such adenomas offers the possibility of a surgical cure. We are reporting a case of Cushing’s syndrome associated with multiple pulmonary adenomas together with severe hypokalemic alkalosis.

Case Report

A 21-year-old white woman was admitted to the United States Public Health Service Hospital January 8, 1962, because of progressive swelling of the face and hands over a three-week period. She had gained 20 pounds, developed acne on the anterior chest, and felt chronically tired during that time. Four months prior to admission, she was treated for “pyelitis,” and a month later delivered a normal girl. At that time, a routine chest x-ray film showed a nodule in the right mid-lung field (Fig. 1). An intermediate PPD skin test was positive, and treatment was started withisoniazid.

Her blood pressure on admission was 200/120, and the pulse rate was 66. Acne vulgaris was present on the anterior chest. Her ankles were edematous. The gluteal folds and upper thighs had numerous striae with light purple discoloration.

Hemoglobin was 12.5 gm., hematocrit 45 per cent, and white blood count 14,790 per cmm. A differential count showed 84 neutrophils, 11 lymphocytes, and 5 monocytes. The urine contained a trace of sugar. The serum sodium, chloride, potassium and CO₂ ranged from 145 to 149 mEq., 85 to 95 mEq., 3.3 to 2.7 mEq., and 29 to 35 mEq., respectively. A fasting blood sugar was 82 mg. per cent; but the two hour value during a glucose tolerance test was 216 mg. per cent. No circulating eosinophils were found, and L. E. preparations were negative. In Table 1 the values, for urinary steroid excretion following various stimulation and suppression tests are given.

The ECG showed depression of S-T segments, lowered T waves and pronounced U waves consistent with hypokalemia. X-ray studies with retroperitoneal injection of CO₂ showed an enlarged left adrenal, and a right adrenal within the upper limits of normal.

With the patient in the prone position the adrenals were exposed simultaneously using posterior paravertebral incisions. After removal of the right adrenal and part of the left, she had cardiac arrest. Cardiac massage, intracardiac adrenalin, and defibrillation were unsuccessful.

Post-mortem Examination

Gross: At necropsy, three pulmonary nodules were found, one in the right middle lobe measuring 0.5 cm. in diameter, one in the left lower lobe 2.0 cm. in diameter, and a third in the left lingula 1.0 cm. in diameter. All were circular, soft, light yellow, encapsulated, and easily shelled away from the surrounding lung parenchyma (Fig. 2). Each was 1.0 to 2.0 cm. deep to the pleural surface. None was grossly related to a bronchus.

The heart was dilated and atonic with petechial hemorrhages over the right and left ventricular surfaces. The right adrenal weighed 32 gm. and the left, 15 gm. The cortex of both glands was thickened. The pituitary weighed 2 gm., the brain, 1040 gm., and the liver, 2300 gm. Except for the lungs and adrenals, all the organs, including the thyroid and ovaries, were macroscopically unremarkable. Microscopic: Sections of the lung nodules showed all three tumors composed of nests of fairly uniform cells with indistinct eosinophilic cytoplasm. Peripheral palisading of nuclei and gland-like spaces were present in a few areas in the largest nodule. The nuclei were in the center of the cells and were fairly large and hyperchromatic (Fig. 3) with only an occasional mitotic figure. The smaller

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Table 1—Steroid Determinations

<table>
<thead>
<tr>
<th>Date</th>
<th>Drug</th>
<th>Urine Volume</th>
<th>17-OH-CS*</th>
<th>17-KS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/23/62</td>
<td>None</td>
<td>2,000 ml.</td>
<td>58.2</td>
<td>42.8</td>
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<tr>
<td>1/24/62</td>
<td>ACTH i.v. 25 units</td>
<td>2,275</td>
<td>69.4</td>
<td>41.0</td>
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<tr>
<td>1/25/62</td>
<td>ACTH i.v. 25 units</td>
<td>3,625</td>
<td>83.0</td>
<td>51.6</td>
</tr>
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<td>1/31/62</td>
<td>2nd day dexamethasone 0.57 mg. q6h</td>
<td>2,015</td>
<td>64.5</td>
<td>49.5</td>
</tr>
<tr>
<td>2/2/62</td>
<td>2nd day dexamethasone 2.07 mg. q6h</td>
<td>3,280</td>
<td>83.5</td>
<td>42.6</td>
</tr>
<tr>
<td>2/5/62</td>
<td>SU-4885 500 mg. q6h</td>
<td>2,625</td>
<td>130.0</td>
<td>51.0</td>
</tr>
<tr>
<td>2/6/62</td>
<td>SU-4885 500 mg. q6h</td>
<td>3,105</td>
<td>131.0</td>
<td>37.5</td>
</tr>
<tr>
<td>2/7/62</td>
<td>SU-4885 500 mg. q6h</td>
<td>2,480</td>
<td>124.0</td>
<td>51.0</td>
</tr>
</tbody>
</table>

*24-hour urinary steroids in mg. per day
**Normal values

Lung nodules were composed predominantly of groups of spindle-shaped cells with elongated nuclei. In these areas, the pattern was similar to that seen in peripheral collections of hyperplastic epithelium in the lungs of occasional cases, the so-called "tumorlets." Other microscopic areas bore a superficial resemblance to oat-cell carcinoma (Fig. 4), but lacked the necrosis, frequent mitoses, and atypism and invasiveness of that tumor. The tumors were surrounded by fibrous capsules; although in some areas there were minute, focal, peripheral infiltrations into adjacent alveolar walls. Sections did not show bronchial epithelium in close relation to the tumors. The stroma was made up of thin septa of loose connective tissue placed between cell nests. The tumor in the left lung had considerably less connective tissue than the others and was more congested. Reticulum was present in the septal connective tissue and perivascular areas. Other special stains, including PAS, mucicarmine, and Fontana yielded no additional information. These tumors were classified as peripheral bronchial adenomas. The largest of the three resembled the carcinoid type, and the others resembled the peripheral adenomas de-

Figure 1: Roentgenogram of chest showing a rounded radiopacity in the right mid-lung field.
scribed by Cohen, et al.  

The heart had hyalinization of some myocardial fibers along with occasional nuclear pyknosis and cytoplasmic vacuolization. The liver showed mild fatty metamorphosis. In the kidneys, mild vacuolar changes were present in the cytoplasm of epithelial cells of the proximal portions of the nephrons. The adrenals showed marked hypertrophy of the zona reticularis. Crooke's changes, consisting of hyalinized basophilic cells with cytoplasmic vacuolization, were present in the pituitary. The spleen had significant depletion of the lymphoid elements. The pancreatic islets were enlarged.

DISCUSSION

Theoretically there are four possibilities to consider when peripheral adenomas of the lung are found in association with clinical hyperfunction of the pituitary or adrenal cortex: (1) the pulmonary adenomas may be incidental; (2) they may themselves produce an ACTH-like substance; (3) overproduction of ACTH or cortisol may have stimulated the formation of the adenomas, and (4) the tumors may secrete a substance which increases pituitary ACTH output. Meador et al. have recently presented evidence that some extra-adrenal tumors associated with Cushing's syndrome may secrete an ACTH-like substance. Similarities in the response to various drugs in our case and those reported by Meador for other functioning tumors suggest that the peripheral bronchial adenomas secreted an ACTH-like substance.

A study of the effect of certain drugs on the urinary excretion of 17-hydroxycorticosteroids (17-OH-CS) is useful in distinguishing between Cushing's disease, and Cushing's syndrome due either to benign adrenal adenoma, carcinoma of the adrenal, or extra-adrenal ACTH secreting tumors. Administration of ACTH produces a definite increase in the urinary 17-OH-CS in patients with Cushing's disease and a slight increase in those with an adrenal adenoma. Patients with ACTH secreting tumors react variably to the test, while those with adrenal carcinomas usually do not show any increase in urinary steroids. Dexamethasone, which suppresses the secretion of pituitary ACTH, indirectly suppresses urinary excretion of 17-OH-CS in patients with Cushing's disease. Dexamethasone suppression tests have no effect on the adrenal carcinomas and ACTH secreting tumors. Methopryapone (Metoprine; SU-4885), an 11 B-hydrolase inhibitor, is used to test the responsiveness of the ACTH regulating mechanism to diminished levels of cortisol. Administration of SU-4885 increases urinary 17-OH-CS in Cushing's disease, produces variable results in ACTH secreting

Figure 2: A low-power view showing the clean line of separation between the collapsed lung tissue in the upper section and tumor nodule on the lower section (H. & E., x80).

Figure 3: A nest of uniform tumor cells showing the large nuclei with slight peripheral palisading. This pattern is somewhat suggestive of the carcinoid type of bronchial adenoma (H. & E., x480).
tumors, and no change in adrenal malignancies.

In our patient, urinary corticosteroid excretion was not stimulated by administration of ACTH or suppressed by administration of dexamethasone. These are the usual findings with an adrenal malignancy. The x-ray film evidence of an enlarged left adrenal also suggested malignancy. In the presence of a functioning, unilateral adrenal carcinoma, the opposite adrenal is usually small. In our patient, however, the right adrenal was at the upper limits of normal. Administration of the SU-4885 produced a distinct rise in the urinary 17-OH-CS and no rise in the 17-KS. In the case of a functioning malignancy of the adrenal cortex, there is usually no elevation of the steroid secretion following administration of SU-4885. The responses of urinary steroid excretion in this patient raised a suspicion of adrenal malignancy in spite of the response to SU-4885. A bilateral adrenal exploration was done, and no cancer was found. Instead, bronchial adenomas were discovered at post-mortem examination.

We speculate, as Meador, et al. did for tumors other than bronchial adenomas, that the bronchial adenomas in this patient probably secreted an ACTH-like substance, but the pituitary was still responsive to a decrease in the level of circulating cortisol. Following the administration of SU-4885, the ACTH production by the tumors, added to the increased amount secreted by the pituitary, stimulated the adrenals to a greater steroid production. Meador, et al. support this hypothesis by cases in which they extracted material with ACTH-like activity from primary and metastatic non-endocrine tumors. Also, their study of the response of ACTH secreting tumors to SU-4885, in Case 2, produced results similar to those obtained in our case.

Hypokalemic alkalosis was also a prominent feature in this patient’s clinical course. Hypokalemic alkalosis may be associated with functioning malignant tumors and Cushing’s syndrome as reported by Kovack and Kyle and Bagshaw. This is the first case of a benign pulmonary tumor associated with Cushing’s syndrome and markedly abnormal serum potassium and CO₂ levels. Although serum aldosterone levels were not determined in our patient, studies on other patients with electrolyte imbalance, and Cushing’s syndrome due to functioning malignancies have given normal values. One can speculate that the low serum potassium and the alkalosis in combination with the prone position used in the posterior approach for adrenalectomy might have contributed to the patient’s irreversible cardiac arrest. The decrease in potassium was probably secondary to excessive secretion of cortisol rather than aldosterone.

Although three pulmonary tumors were present at post-mortem examination, there was x-ray evidence of only a solitary pulmonary lesion in the right mid-lung field. If the clinically apparent adenoma had been removed, the Cushing’s syndrome would probably have persisted until the other two adenomas had been removed. The experience gained from this case points to the necessity of exploratory thoracotomy when undiagnosed pulmonary nodules are associated with bilateral adrenal cortical

![Figure 4: One area of the right lower lobe adenoma showing small, elongated cells, with very little cytoplasm. The pattern superficially resembles an oat-cell carcinoma, but necrosis is lacking and mitoses are sparse (H & E, x120).](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21407/ on 05/30/2017)
hyperplasia and Cushing's syndrome. In addition, when a functioning bronchial adenoma has been recognized, the possibility should be kept in mind that additional, clinically unrecognized, bronchial adenomas may be present.

Histologically, two of the bronchial tumors were similar to the single adenomas described by Cohen et al. They did not present the classic pattern seen in the carcinoid or cylindromatous varieties. The location of the tumors is interesting in that one was in the lingula of the left lung, the site of two previously reported cases. The superficial resemblance of the bronchial adenomas to epithelial thymomas and oat-cell carcinomas led Cohen to suggest that these three types of tumor associated with Cushing's syndrome may have a common cell of origin.

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References

For reprints, please write Dr. Sobota, Tulane University Medical School, New Orleans.

COURSE FOR INHALATION THERAPISTS

The University of Chicago Hospitals, School of Inhalation Therapy, will present a course in Respiratory Physiology for Inhalation Therapists, to be held at the University of Chicago Center for Continuing Education, October 2-4, 1964. The course will consist of lectures and round table conferences on the physics, anatomy and physiology of normal respiration and the pathophysiology of respiratory diseases. Tuition for the course is $25 which includes registration, syllabus of essential material of the course, course materials, a banquet and luncheons. Please address inquiries and registration requests to: Mr. Claude Well, Center for Continuing Education, 1307 East 60th Street, Chicago, Illinois 60637.

CONFERENCE ON BIOLOGIC EFFECTS OF ASBESTOS

The New York Academy of Sciences will present a Conference on the Biologic Effects of Asbestos, to be held in New York City, October 19-21, 1964. The program will include reports of current investigations from the United States, Canada and other countries. There is no registration or other fee, but attendance is by invitation only and such invitation is limited to members of the Academy and to interested members of the medical and biologic sciences. Invitations will also be available to active workers in allied fields. Requests for information and invitation should be addressed to Dr. Irving J. Selikoff, Chairman, Conference on Biologic Effects of Asbestos, New York Academy of Sciences, 2 East 63rd Street, New York 21, New York.