Hormone Producing Tumors of the Lung

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ABSTRACT

With the report of the production of ACTH by non-endocrine neoplastic tissue, Meador and associates set the stage for an increasing clinical awareness of ectopic hormone production from a variety of neoplasms. The clinical syndromes are those expected from excess secretion of ACTH, ADH, parathyroid hormone, growth hormone, insulin and other substances. At times, however, the presence of ectopic hormone production is masked by other features of the patient's illness or because the lung tumor produces more than one hormonal substance. Clinical appreciation of this entity coupled to the greater availability of immunoassays for measurement of hormones in blood and tumor extracts can be expected to increase the clinical pathologist's recognition of these syndromes. More thorough tabulation of the true incidence of ectopic hormone production from lung cancers and careful measurement of the spectrum of hormone production by such tumors should help to unravel some of the many questions concerning the pathogenesis of hormonal secretion from non-endocrine tissues.

With their report in 1962 of the production of ACTH by nonendocrine neoplastic tissue, Meador et al set the stage for an increasing clinical awareness of ectopic hormone production and diverse endocrinologic and metabolic syndromes in patients with a variety of neoplasms. Hormonal secretion from pancreatic, renal, bladder, ovarian, prostatic, parotid, gastric, thymic and pulmonary tumors has been reported. Secretion of more than one hormonal substance by a neoplasm has been found in select cases.

Ectopic Secretions

Ectopic secretions from primary lung tumors (table I) have included ACTH, anti-diuretic hormone (ADH), parathyroid hormone (PTH), insulin, serotonin, gonadotrophins, histamine, somatomamotropin, growth hormone and melanocyte stimulating hormones. Certain tumors appear to synthesize and secrete hormones which resemble hypothalamic pituitary release factors. These materials may simultaneously stimulate peptide hormone syn-

| TABLE I |
| Ectopic Hormone Production from Lung Tumors |
| ACTH (MSH) | Serotonin | Lactogen |
| ADH | Histamine | Growth Hormone |
| PTH | Insulin | Gonadotrophin |
TABLE II
ENDOCRINE SYNDROMES REPORTED IN LUNG TUMOR PATIENTS

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Urticaria</th>
<th>Acromegaly</th>
<th>Gynecomastia</th>
<th>Hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cushing's</td>
<td>Dilutional state</td>
<td>Hypercalcemia</td>
<td>Carcinoid</td>
<td></td>
</tr>
</tbody>
</table>

thesis within the tumor and cause pituitary release of, for example, ACTH or growth hormone.6

The true incidence of these syndromes is not clearly known since the associated signs and symptoms of hormone excess and metabolic disturbances resulting therefrom may be easily masked or attributed to the patient's underlying terminal malignant illness. Furthermore, documenting the actual incidence will depend upon the surgeon's, the internist's and the pathologist's awareness and interest in these syndromes.

Although virtually all types of lung tumors have had ectopic hormone production ascribed to them, bronchial carcinoids and oat cell carcinoma have been the most frequent. By and large, ACTH production has been associated with oat cell carcinoma and bronchial adenoma. The hyponatremia syndrome of excess ADH production is associated with both squamous cell carcinoma and oat cell carcinoma. Hypercalcemia, secondary to secretion of a material with the immunologic and biologic actions of parathyroid hormone, has been noted more often in patients with squamous cell carcinoma of the lung.2

Clinical Syndromes

The clinical syndromes resulting from ectopic hormone production (table II) of one or more hormones from tumors of the lung are many. Since certain tumors may produce more than one substance, the syndrome may be bizarre indeed, as in a patient who had co-existing adenocarcinoma of the bronchus, carcinoid syndrome, Cushing's disease, and recurrent urticaria.6 Furthermore, even if due to excess production of a single peptide, almost indistinguishable immunologically and biologically from its native endocrine source, the resulting clinical manifestations may be quite different. The constitutional manifestations of malignant disease may overshadow obvious clues of excessive peptide hormone production. In Cushing's disease, for example, secondary to ACTH production from a far advanced lung cancer, the characteristic habitus of Cushing's syndrome may be altogether lacking. Severe hypokalemic alkalosis and myopathy may predominate in such cases.6 Conversely, the true ectopic nature of an endocrine syndrome may be missed. Several patients harboring ACTH producing bronchial carcinoids, for example, underwent adrenalectomy months to years before the lung neoplasm was discovered and the accurate cause of the Cushing's disease established.14

In addition to Cushing's disease, excessive production of antidiuretic hormone and hypercalcemia with hypophosphatemia, several instances of the carcinoid syndrome have been described.1 This syndrome may even co-exist with Cushing's disease.8 A single instance of a hypoglycemia syndrome in a patient whose lung cancer contained large amounts of immunoreactive insulin has been reported.11 Several patients with lung cancer had gynecomastia, spider nevi and high plasma estrogen levels. In a few who were studied, high urinary and blood gonadotrophin titers were discovered.4,8 At autopsy, tumor tissue was also found to contain high levels of gonadotrophin substances. In this syndrome, it is assumed that the clinical manifestations of hyperestrogenism result from gonadotrophin stimulation of testicular and perhaps adrenal estrogen secretion. Lung tumors which have contained high levels of somatomammotrophin, placental lactogen, have also been
reported but no obvious clinical syndrome was evident in these patients.\textsuperscript{16} There have been two reports of the disappearance of acromegaly after removal of a bronchogenic carcinoma. In both patients, raised growth hormone levels returned to the normal range after the operation.\textsuperscript{5,12} In one instance, tissue was not assayed so that it was not possible to be certain that excess growth hormone secretion by the tumor caused the acromegaly. In another, assay of the tumor did not reveal the presence of growth hormone; some data from this latter case suggested the tumor might produce a material which stimulated either the hypothalamus or pituitary directly to secrete excess levels of growth hormone. Finally, the pulmonary osteoarthropathy and clubbing which occur in many patients with lung neoplasms is suspected to be hormonally mediated because of its striking disappearance after successful removal of the lung tumor; however, no hormonal substances has been identified in such cases.

Ectopic production of parathyroid hormone, antidiuretic hormone, ACTH and serotonin have been encountered most frequently in lung tumor patients. The resulting clinical syndromes are largely those anticipated from excess levels of any one of these potent factors. Certain features may help to distinguish ectopic from true glandular secretion of a particular hormone but at times, when the pulmonary growth is small, it may be impossible to arrive at the correct diagnosis.

**Cushing's Disease**

Ectopic production of ACTH by oat cell carcinomas or bronchial carcinoids and, far less frequently, pulmonary squamous cell carcinomas or adenocarcinomas has been reported.\textsuperscript{5,8} The resulting clinical syndrome may entirely mimic pituitary-induced bilateral adrenal hyperplasia; indeed, as noted earlier, there are recorded examples of patients who have undergone adrenalectomy with discovery of the bronchial carcinoid months to years later.\textsuperscript{14} In patients with lung carcinomas causing adrenal hyperplasia and Cushing's disease, several features serve to alert the physician to the underlying course of excess ACTH (table III).\textsuperscript{8} Males predominate, wasting is clearly evident and the characteristic habitus of Cushing's disease is almost always lacking. The clinical course is often fulminant with sudden appearance of florid, insulin requiring diabetes mellitus. Patient disability is severe and impressive hypokalemic alkalosis and myopathy are prominent. Edema is frequently present and seldom is seen in patients with pituitary-caused hypercortisolism. In addition to the more marked hypokalemic alkalosis, suppression and stimulation tests may help to distinguish between true pituitary-Cushing's disease and the ectopic syndrome. Dexamethasone, in the amount of 8 mg, will effectively subdue overproduction of ACTH from the pituitary in patients with true Cushing's disease and thus a marked fall will take place in urinary 17-ketosteroids and hydroxycorticosteroid levels. (Normal secretion will be suppressed with 2 mg dexamethasone daily.) In the patient with an ACTH producing bronchogenic tumor, hormone secretion may be suppressed but less frequently than in classic Cushing's disease. Lung cancers may not be suppressed at all. Administration of metapyrone, a beta-hydroxylase inhibitor of glucocorticoid synthesis, will cause further secretion of ACTH from the pituitary in the true Cushing's disease patient. This will cause increased levels of

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**TABLE III**

**Distinguishing Features**

<table>
<thead>
<tr>
<th>Ectopic ACTH Syndrome</th>
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<tbody>
<tr>
<td>Males; short history; myopathy; hypokalemic alkalosis; edema; prominent diabetes;</td>
</tr>
<tr>
<td>17OHC secretion not influenced by ACTH, Metyrapone or Decadron</td>
</tr>
</tbody>
</table>

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plasma corticoids and urinary 17-hydroxy-corticosteroids, a response not seen in patients with lung cancers which produce ACTH. This observation serves to support the suspicion that true Cushing's disease is the result of a relatively insensitive hypothalamic locus responsible for secretion of corticotrophin releasing factor. Since ACTH production from these lung tumors is not under hypothalamic control, reducing the rate of cortisol synthesis by administering metapyrone has little if any effect on further adrenal secretion of corticoids. Histologic examination of adrenals from a patient with the ectopic ACTH syndrome may fail to reveal the wide zone of lipid rich cells characteristic of classic Cushing's disease, and an observant pathologist may suggest the ectopic possibility to the clinician on this basis.

Treatment of this syndrome is either removing the source of excess ACTH or the hyperplastic adrenal glands. In patients too ill for major surgical intervention, it is possible to resort to medical approaches to combat hypercortisolism. Dilantin, in some patients, hastens hepatic catabolism of cortisol. Metapyrone and aminoglutethimide partially block steroid synthesis and the insecticide o,p'-DDD, a poison, destroys adrenal tissue.

Excess ADH Secretion Syndrome

The hallmarks of this syndrome are a dilutional state with marked hyponatremia, natruresis and a urine osmolality significantly greater than that of serum. The hyponatremia can be so severe as to cause convulsions. This syndrome must be distinguished from that of inappropriate antidiuretic hormone secretion from the posterior pituitary seen in patients with intracranial disease, hypopituitarism with ACTH deficiency, hypothyroidism or a wide variety of pulmonary diseases. In the ectopic syndrome, removal of the offending tumor or water restriction will correct the electrolyte abnormality. Administering parenteral saline will not alleviate the problem since a pronounced natruresis continues and greater dilution may even occur. Because total body sodium chloride stores are basically depleted, the administration of naturetic diuretics will do little and may make the condition worse.

Tumor Production of a Parathyroid Hormone Substance

In men over 50 years of age with hypercalcemia and hypophosphatemia without evident renal stones or metabolic bone disease, the possibility of an underlying occult neoplasm must be given serious consideration. Lung cancer, often a squamous cell carcinoma of the bronchus, may produce a substance with biologic and immunologic characteristics almost identical to native parathyroid hormone. Before long it may be possible to separate with confidence neoplasm parathyroid hormone from glandular PTH by using more specific antisera.

The major consequence of ectopic production of parathyroid hormone from a lung tumor is hypercalcemia which obtunds the central nervous system and causes fatigue, lethargy and pseudoileus with constipation and anorexia. Nausea and vomiting may also be prominent signs. Hypercalcemic nephropathy results in failure of the kidneys to concentrate urine with the result that the polyuric, anoretic, nauseated patient becomes progressively dehydrated and debilitated. The usual measures for treating hypercalcemia, if effective, will ameliorate most if not all of these signs and symptoms. Fluids, activity, low dietary calcium, anabolic steroids and, when warranted, Mithramycin or inorganic phosphates may be used therapeutically.

The Carcinoid Syndrome and Lung Tumors

Excessive production of 5-hydroxyindolacetic acid and serotonin from bronchial
carcinoids and oat cell carcinomas may be associated with one or more of the clinical features of the carcinoid syndrome. These signs and symptoms may extend over years and not give rise to an accurate diagnosis if the clinician is unsuspecting and the lung lesion too small to be seen on X-ray. Symptoms include vasomotor instability with episodes of bizarre flushing, hyperperistalsis, diarrhea, hypotension, dizziness, bronchospasm with or without audible wheezing and progressive weight loss, often attributable to anorexia and nausea. When lung tumors produce this syndrome, characteristic left-sided heart lesions develop. On auscultation, these sound like typical rheumatic valvular disease but when examined post-mortem, a peculiar type of fibrous tissue, characteristic of the carcinoid syndrome, is deposited on the mitral and aortic valves and over the endocardium of the atrium and left ventricle. Urinary-5-hydroxyindolacetic acid excretion exceeds 10 to 15 mg per day. The syndrome may be treated effectively if the source of excess serotonin producing tissue can be removed surgically. Otherwise, a variety of serotonin antagonists or partial inhibitors of serotonin synthesis may be used with variable success.

Single case reports of ectopic hormone production from lung tumors are still appearing in the literature. Larger series are being reported, however, from pathology laboratories wherein the interested pathologist discovers ectopic hormone production after the fact. By taking note, for example, of hyperplastic adrenals at autopsy, and coupling this to tumor and blood assays for ACTH and to data from the patient's chart, an observant pathologist may make the diagnosis of an ectopic hormone syndrome at post-mortem. Clearly, the frequency of these syndromes may change as pathologists become increasingly aware of this entity and begin to tabulate findings from post-mortem material in a more coordinated fashion, utilizing the clinical record and assay of blood and tumor extracts by immunoassays now more generally available.

Why should neoplasms have the ability to produce peptide and amines hormones? Many theories have been advanced. One which is gaining interest is the notion that hormone secreting cells are not endodermal but rather of neural crest origin. This theory proposes that, during embryogenesis, these cells stream caudally and nests are deposited in the bronchi, in the digestive tract, pancreas and elsewhere. Neoplasms arising from these cells are equipped with the potential for producing many peptide hormones as well as biogenic amines. This theory, if proven correct, would go a long way towards helping to explain both ectopic hormone production from malignancies and the peculiar occurrence of multiple endocrine tumors, the polyglandular syndrome.

References

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“The most beautiful thing we can experience is the mysterious. It is the source of all true art and science.”

Albert Einstein (“What I Believe”)