

The Pattern of Ectopic Hormone Production in Lung Cancer

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Pulmonary cancers produce many hormonal polypeptides. There is a tumor-specific pattern to the appearance of abnormal adrenal function and inappropriate secretion of vasopressin, which are frequently found in small cell undifferentiated carcinoma but occur only very rarely, if at all, in squamous tumors. Humoral hypercalcemia, on the other hand, occurs almost entirely in squamous tumors and is rarely if ever seen in small cell or large cell tumors or in adenocarcinoma. In contrast, "big ACTH" and beta lipotropin are found in the plasma and tumor extracts of lung cancers of all types. Calcitonin and the beta chain of human chorionic gonadotropin are also found in the plasma of a considerable portion of patients with all histological types of lung cancers.

The association of certain pulmonary neoplasms with hormonal syndromes has been recognized for at least 50 years [1], and the fact that such syndromes result from release of polypeptide hormones by the tumor has been known for at least two decades [2,3]. The fact that the hormones originate in tumors arising in tissue which does not usually secrete endocrine substances led to their being called "ectopic" [4]. Since the discovery of this property of tumors, an immense literature has built up, reporting individuals or small groups of patients with the syndromes produced by ectopic hormones. Within the past five years or less, the possibility of utilizing the production of such hormones as markers in diagnosing pulmonary tumors and following their response to treatment has led to active interest in the levels of these substances in the plasma of patients with pulmonary neoplasms. It is somewhat surprising, therefore, that very few studies have been published in which an attempt has been made to study populations of patients with carcinoma of the lung in order to determine the distribution and frequency of the production of hormones by tumors of various types. In this paper an attempt is made to survey the present state of the problem in order to determine whether there is a characteristic distribution pattern of hormones produced by lung tumors according to their histological classification. The question of whether measurement of such hormones is helpful in following the clinical course of the patients will not be discussed, since it has been considered elsewhere [5,6].

The literature was surveyed for studies in which an attempt had been made to investigate all patients with carcinoma of the lung entering the clinic or hospital. In some instances, the survey was limited to a particular type of tumor (usually small

cell undifferentiated carcinoma) and these were accepted provided it appeared that all patients with the diagnosis had been included. Reports were rejected if the authors had investigated only or chiefly patients with clinical endocrine syndromes, or if the histological classification of the patients was not indicated.

In many instances the survey was limited to measurement of plasma hormones by radioimmuno- or bioassay, but in others physiological investigations were also used to seek evidence for abnormal control of such variables as plasma cortisol, serum calcium concentration and plasma, and urine osmolality or urine volume. The diagnosis of abnormal adrenal cortical control was based on loss of diurnal variation or suppressibility of plasma cortisol concentration with dexamethasone. The diagnosis of SIADH was based on hemodilution combined with high urinary osmolality.

The results are shown in the tables. Table 1 shows the frequency with which abnormalities of adrenal function, vasopressin secretion, calcium concentration, plasma calcitonin, and beta HCG were observed in each histological type of tumor. Note that abnormal adrenal function and SIADH were observed very frequently in small cell tumors and never in squamous tumors, whereas hypercalcemia was common in squamous but absent in small cell neoplasms. Calcitonin and hCG were often increased in all types of tumors.

Ever since the work of Gerwitz and Yalow [8] there has been interest in whether metabolic precursors of ACTH such as "big" ACTH or beta lipotropin might be useful as tumor markers. Table 2 shows the results of studies using the special methods necessary for detection of these moieties. Because Yalow's group has been interested in comparing tumor and plasma levels, they have not studied many patients with small cell tumors. Surgery is seldom performed in this group, so tissue adequate for measuring tumor hormone concentration is seldom available. The limited number of small cell tumors reported in the table reflects this research strategy [9].

Table 1 probably presents a minimal value for the incidence of the abnormalities mentioned, because most surveys obtained their data on only one occasion during the patients' course. An abnormality developing at some other time during the disease might therefore have been missed. Moreover, some abnormalities are demonstrable only after tests which stress or manipulate the system under study. For example, the incidence of the syndrome of inappropriate vasopressin secretion (SIADH) may become apparent only when a patient with mildly depressed plasma osmolality is subjected to a water load [12]. Surveys depending entirely on a single measurement of ACTH concentration may be misleading. It is well known that the plasma ACTH normally varies rapidly over a wide range, so even in a patient ordinarily having a slightly elevated hormone concentration it is possible that a single determination might fall within the normal range. Moreover, if a substantial portion of the circulating ACTH originates in the tumor, the normal control mechanisms producing diurnal rhythmicity and feedback suppression might be lost although total ACTH is within normal limits [11,12]. ACTH samples obtained late in the day should have a higher discriminating value than those taken early in the morning because of diurnal variation of normal pituitary secretion of ACTH, but Yalow's group [9] seems to be the only one taking advantage of this fact.

Experienced pathologists often disagree in classifying tumors, especially when the specimen contains more than one type of tissue. The differentiation of a highly anaplastic squamous tumor from a small cell cancer may occasionally depend on the presence of only a few strands of keratin. Whether such a tumor ends up in the small cell or squamous category depends to some extent on whether the pathologist bases

TABLE 1
Relationship of Cell Type to Ectopic Hormone Production

Hormone	Cell Type				References
	Small Cell	Squamous	Adenocarcinoma	Large Cell	
ACTH					
Abnormal control pattern					
or ACTH > 80 pg/ml	69/190 (36%)	0/36	5/20 (25%)		[6,10,11,12]
Ectopic ACTH					
Syndromes	9/202 (5%)	0/36	0/20		[6,12,13,14]
Vasopressin					
SIADH	60/264 (23%)	0/18	3/12 (25%)		[7,10,12,13,14,15]
Calcitonin	116/226 (51%)	28/137 (20%)	20/60 (33%)	8/24 (33%)	[6,7,10,12,16,17,18,19,28,*]
Humoral hypercalcemia (no bone metastases)	0/112	15/60 (25%)	0/20	2/32 (6%)	[12,20,*]
beta-HCG	18/130 (19%)	8/62 (13%)	11/45 (24%)	1/11 (9%)	[6,10,21,22,*]

* Bondy PK: Unpublished data.

TABLE 2
 "Big" ACTH and beta LPH as Markers of Lung Cancer

Cell Type	ACTH > 100 pg/ml			beta LPH > 60 pg/ml		
	No. positive	No. examined	% positive	No. positive	No. examined	% positive
Small Cell	17	27	63	13	24	54
Squamous	79	86	92	10	30	33
Adenocarcinoma	32	40	80	20	20	100
Large Cell	7	11	64			

Source: [9,11,27]

his classification on the most differentiated portion of the tumor or on the average appearance. Electron microscopy may be valuable in identifying the "APUD" cells which produce the small cell secretory pattern [23], but most authors did not mention using this modality.

Considering these problems, it is interesting that the histological classification of types of pulmonary neoplasms in several different clinical centers produced such a clear pattern of association of abnormal adrenal control, SIADH, and humoral hypercalcemia with specific types of tumors. It appears that these three determinations can discriminate between small cell and squamous tumors, and could be used to bolster a diagnosis based on histology or to predict the histology (and therefore the response to treatment) if tissue is not available. The hormones appear to be of less differential value in adenocarcinoma, but the number of observations is small. Calcitonin is not of much value in differential diagnosis, although it has been recommended for following the response to treatment [6]. It should also be remembered that many of these hormones may be increased for other causes than secretion by the tumor. SIADH can be caused by nonmalignant disease of the lungs, especially infection [24] and ACTH is secreted in response to a variety of stresses [25].

There is general agreement that in patients with carcinoma of the lung the syndrome of ectopic ACTH production occurs mainly, if not uniquely, in small cell tumors. The data in Table 2 are interesting, therefore, because they suggest that all lung tumors contain and may release a non-functional form of ACTH, which may be a pro-ACTH ("big" ACTH) or the larger precursor polypeptide, beta lipotropin. This polypeptide includes ACTH in its amino acid sequence together with the endorphins and melanocyte stimulating activity. Aside from its ability to produce darkening of the skin, beta lipotropin is not known to have any physiological activity, in spite of the powerful effects produced by its fragments. It is possible that most lung tumors can produce the precursor but only the small cell tumor can break it down to functional units [26]. In any case, there is a clear clinical difference between the probable diagnosis of small cell tumor in the presence of an abnormality of adrenal function and the demonstration of some form of "big" ACTH or beta lipotropin [9,11,27] in the plasma of patients with lung tumors regardless of histological type. The general presence of "big" ACTH in all types of lung cancer is reminiscent of the beta chain of human chorionic gonadotropin, which has been found in an ineffective form in normal tissue and most tumors [29] and may therefore be of some value in diagnosing cancer, but not in distinguishing one tumor from another.

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