Human Chorionic Gonadotropin as a Tumor Marker

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ABSTRACT

Ectopic production and secretion of hormones by a wide variety of tumors has been known for decades. Initially, ectopic hormone secretion was recognized by signs and symptoms of excess circulating biologically active hormone. With development of more sophisticated assay techniques, biologically inactive fragments and “big” forms of authentic hormones have been identified in these syndromes.

Recently, a specific hCG assay has been developed for selectively measuring hCG in plasma samples containing both hLH and hCG. Studies reported to date suggest that hCG may be a good tumor marker. Using that assay system, several hundred sera obtained from patients with a wide variety of tumors were screened. Patients with tumors of the stomach, liver, ovary and testis were found to have the highest incidence of ectopic hCG secretion.

Introduction

A wide variety of tumors of non-endocrine organ origin secrete varying quantities of biologically active hormones. The ectopic hormone production by those tumors was initially recognized by the clinical signs and symptoms resulting from excess circulating biologically active hormone. In fact, every known glycoprotein and polypeptide hormone normally secreted by the pituitary or pancreas has been immunologically or biologically identified in these syndromes.

Some hormones have been more frequently identified in these syndromes. Ectopic secretion of a specific hormone is frequently more commonly identified with a specific cell type or germinal layer derivative. In table I is summarized the most commonly found hormones and accompanying syndromes associated with ectopic polypeptide hormone secretion.

Altered Hormonal Forms

With the advent of more sophisticated techniques, it has become apparent that not all tumors secrete biologically active hormones. Although a polypeptide hormone may be detectable at low levels immunologically, the concentration of the hormone may not be sufficiently high for inducing clinical signs and symptoms. On
the other hand, an altered form of a polypeptide hormone may be detectible with conventional immunologic techniques but be biologically inactive. Therefore, only by routine screening of patients with those tumors which are more commonly associated with ectopic secretion of a given hormone will the true incidence of ectopic production by a specific tumor type be known.

Thirty of 31 patients with metastatic lung tumors secreted biologically inactive “big” ACTH which was immunologically similar to native ACTH. The “big” ACTH could be converted into a biologically active form with rapid tryptic digestion. Half the patients with non-metastatic lung cancer had serum ACTH levels equal to or greater than 150 pg per ml as opposed to 6 percent of controls who had comparable blood levels in that study. In addition to ACTH that is indistinguishable from authentic pituitary ACTH, tumors may contain N- and C-terminal fragments of authentic ACTH. In addition to “big” ACTH, large varieties of other hormones have been identified in patients with tumors of endocrine organs,—for example, the pancreas and parathyroids.

Development of specific and sensitive radioimmunoassays for the various polypeptide hormones has enabled investigators to identify readily patients with tumors ectopically secreting hormones. However, in order to make a definitive diagnosis, the hormone must be extracted from the tumor tissue or a hormonal gradient be demonstrable across the tumor bed.

**Specific Human Chorionic Gonadotropin (hCG) Assay**

Unlike the polypeptide hormones of the pituitary, pancreas or parathyroids, human chorionic gonadotropin does not circulate except during pregnancy. Human chorionic gonadotropin and human luteinizing hormone (hLH) are two glycoprotein hormones with similar biologic activities. Both hormones are composed of two subunits, α and β. As is the case for the other human glycoprotein hormones, the β subunit confers immunologic and biologic specificity. The β subunit of hCG shares 80 percent homology with the β subunit of hLH. All known clinical radioimmunoassay systems using antisera raised to either native hCG or hLH cannot discriminate between those two hormones if they are present in the same sample.

Although hLH and hCG have similar biologic and immunologic activities, antisera generated to the β subunit of hCG discriminate between hLH and hCG immunologically. Using one of those antisera, a specific hCG assay was developed for selectively measuring hCG in patient samples containing both hLH and hCG.

All assay tubes, including “blank” and “100 percent” tubes, must contain an equal volume of human plasma in order to obviate a non-specific plasma protein effect in that assay system. Either hCG or its β subunit may be radio-labeled by a modified chloramine-T method. Greater precision and sensitivity result when 125I-hCG is the labeled ligand. Highly purified hCG served as reference preparation. The assay tubes initially incubated at 37° for two hours, then incubated for a minimum of 15 hours at 4°. Second antibody, sheep anti-rabbit gamma globulin, was added and the assay tubes incubated an additional 6 to 10 hours. After centrifugation at 2500 rpm for 15 minutes, the supernatant was aspirated.

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**Table I**

<table>
<thead>
<tr>
<th>Ectopic Hormone</th>
<th>Syndrome</th>
<th>Tumor*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH</td>
<td>Cushing's</td>
<td>Lung, thymus, pancreas, thyroid, phaeochromocytoma</td>
</tr>
<tr>
<td>hCG</td>
<td>Precocious puberty, gynaecomastia</td>
<td>Gastrointestinal tract, lung, melanoma, gonad</td>
</tr>
<tr>
<td>Parathormone</td>
<td>Hypercalcaemia</td>
<td>Lung, kidney, liver, gonad</td>
</tr>
<tr>
<td>ADH</td>
<td>Inappropriate antidiuresis</td>
<td>Lung, pancreas</td>
</tr>
</tbody>
</table>

*Organ most frequently associated with ectopic secretion of the indicated hormone.
and the pellet (bound hormone) counted. This assay system permits an investigator to measure selectively hCG in patient samples containing both hLH and hCG. Several hundred tubes can be assayed within a two-day period.

**Ectopic Gonadotropin Secretion**

Patients with ectopic gonadotropin secretion were initially recognized by clinical syndromes. The first case of precocious puberty ascribed to ectopic gonadotropin secretion by a hepatoblastoma was reported nearly twenty years ago. Gyneecomastia has been described in patients with lung tumors, melanomas and adrenal tumors associated with supraphysiologic quantities of gonadotropin in 24 hour urine collections. However, the true incidence of physical stigmata associated with ectopic gonadotropin secretion is yet to be determined. It is not clear whether or not the gynecomastia in patients with gonadotropin secreting tumors is related to gonadotropin or some other factor secreted by tumors. Both men with testicular tumors secreting hCG and infertile men treated with exogenous hCG develop gynecomastia. Whether or not the gynecomastia is an effect of hCG, contaminant (some factor not currently recognized as a polypeptide hormone which can induce gynecomastia) or another hormonal polypeptide is not clear.

**Nature of Ectopic Gonadotropin**

Until recently, the nature of the secreted gonadotropin was unknown. Initial studies relied on biologic end points which could not discriminate between the physiologic effects of hLH and hCG. However, biologic end points could discern the differential effects of luteinizing activity induced by hLH or hCG from the physiologic effects of follicle stimulating hormone, another gonadotropin. Even after the more sensitive radioimmunoassay techniques became available, the nature of the gonadotropin in those syndromes remained unknown. The recent development of a sensitive and specific radioimmunoassay for hCG, has permitted investigators to screen large numbers of plasma or serum samples from patients with a wide variety of tumors. High levels of hLH found in women and castrate men do not interfere in this assay.

**Incidence of Ectopic hCG Secretion**

In table II is summarized the incidence of ectopic hCG secretion in a wide variety of patients with documented neoplasms. As one would expect, all women with untreated gestational trophoblastic disease had clearly detectible hCG. The greater sensitivity of this specific hCG radioimmunoassay undoubtedly accounts for the higher percentage of patients with testicular neoplasms having measurable hCG. In previous studies in which less sensitive techniques were used, only 13 percent of patients with seminomas and 30 percent of patients with embryonal carcinomas excreted gonadotropin levels in excess of that expected from pituitary secretion alone. With the present assay technique, 37.5 percent of patients with seminomas and 56 percent of those with embryonal carcinomas had clearly detectible circulating hCG.

In our initial report, six patients with adenocarcinoma of the ovary were screened. None of those patients had measurable hCG. The author and co-workers have now sampled a larger population of women with ovarian tumors and have found a significant number of them with tumors ectopically secreting hCG (table II).

The relatively high percentage of patients with tumors of the liver or gastrointestinal tract with measurable hCG was surprising. The highest incidence was found in patients with adenocarcinomas of the stomach and hepatomas. In fact, patients with adenocarcinomas of the stom-
ach have had the highest circulating levels of hCG of all types screened. In some cases, the hCG levels have approached those found in the first trimester of pregnancy.

Other Placental Tumor Markers

Ectopic production of at least two other placental substances has been described. Human chorionic somatomammotropin (hCS) shares immunologic and biologic similarities with its pituitary counterpart, human growth hormone. Ectopic hCS production has been described in a variety of tumors, most commonly lung. A placental isoenzyme of alkaline phosphatase (PAP) has been detected in sera of patients with a wide variety of tumors. However, the overall incidence of detectable PAP was less than 5 percent.

Specific assays have been developed for most of the hormonal peptides ectopically secreted by a wide variety of tumors. Ectopic hormone secretion by tumors may serve as a diagnostic clue to occult neoplasms. In some cases, the tumor "marker" may be used for monitoring therapy as well as detecting recurrent disease.

References


