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Human chorionic gonadotropin measurements in parathyroid carcinoma

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Abstract

Objective—Preoperatively, it is difficult to differentiate between parathyroid cancer (PtCa) and severe primary hyperparathyroidism (PHPT) due to a benign tumor. Human chorionic gonadotropin (hCG) is a tumor marker in trophoblastic and nontrophoblastic cancers and hyperglycosylated hCG is increased in hCG-secreting malignancies. We investigated whether hCG can distinguish PtCa cancer from benign disease and add prognostic information.

Design—Observational study.

Methods—Measurement of urinary hCG (total and malignant isoforms) and serum malignant hCG in 8 subjects with PtCa and in 18 subjects with PHPT (measurement of urine in ten and serum in eight).

Results—Total urinary hCG was normal in the benign PHPT control subjects (range: 0–17 fmol/mg Cr; $nl < 50$). In the PtCa subjects, three had normal total urinary hCG levels and survived complication free for at least 2 years; three had persistently elevated total urinary hCG levels (range: 217–1986 fmol/mg Cr) and sustained hip fracture ($n = 3$) and died ($n = 2$) within 3 and 6 months respectively; two had a rise in total urinary hCG and had hip fracture ($n = 1$) and died ($n = 2$) within 4 and 10 months respectively. Elevated urinary hCG was of the malignant hyperglycosylated isoform. Serum malignant hyperglycosylated hCG values in all of the cancer patients exceeded the maximal serum malignant hCG level of the PHPT subjects with benign disease (3.77 pmol/l).

Conclusion—hCG, especially its hyperglycosylated isoform, might add diagnostic and prognostic information in PtCa. Further studies would help to elucidate the role of hCG as a potential tumor marker in this disease.

Introduction

Parathyroid carcinoma is a rare presentation of primary hyperparathyroidism (PHPT) (1). In most patients with PHPT today, the disease is benign and asymptomatic. Nevertheless, PHPT is still occasionally seen in the more classical form in which severe biochemical and clinical

Declaration of interest

The authors declare that there is no conflict of interest that would prejudice the impartiality of this scientific work.

manifestations predominate. In these patients, a high index of suspicion for parathyroid cancer (PtCa) is important, because the best chance for cure is associated with complete resection at the time of initial surgery (2–5). However, on clinical grounds alone, it is very difficult to distinguish between very active benign parathyroid disease and its malignant counterpart. A mutation in a tumor suppressor gene, *HRPT2*, has been demonstrated in many cases of parathyroid carcinoma (6). While further studies are ongoing to determine the clinical utility of *HRPT2* and its encoded parafibromin measurements, a readily available biochemical marker that reliably distinguishes between malignant and benign parathyroid disease would be useful.

Human chorionic gonadotropin (hCG), a glycoprotein hormone, is normally produced by placental trophoblasts. However, sera from many patients with trophoblastic and certain nontrophoblastic tumors also contain hCG immunoreactivity, usually of the free β -subunit (7). In hCG-secreting malignancies, an isoform of hCG that is hyperglycosylated is preferentially secreted (8,9). In these diseases, elevated expression of standard or hyperglycosylated hCG is an adverse prognostic indicator and helps to predict recurrence (7).

In the course of a therapeutic trial with the calcimimetic, cinacalcet, we discovered among baseline indices elevated levels of hCG in the serum of non-pregnant women and men with PtCa. This unexpected observation raised the possibility that hCG is a marker for PtCa and might correlate with disease activity. The purpose of this paper is to report findings that support this hypothesis.

Methods

Subjects

Eight consecutive patients with PtCa and unknown hCG levels were recruited and enrolled. Five of the cancer patients had histological features at initial parathyroid surgery, which were consistent with carcinoma; of those five, four had either concomitant or subsequent metastatic disease (mediastinal and lung) while the other subject had persistent hypercalcemia (> 3.5 mmol/l) and high parathyroid hormone (PTH) levels (> 100 pmol/l). The other three cancer patients had initial histological features that were consistent with parathyroid adenomas, but had recurrences of hypercalcemia with subsequent surgeries and histological findings consistent with PtCa, as well as neck metastases in two of the patients. Parathyroid carcinoma was thus confirmed on histology in all of the patients, either on initial or repeat parathyroid surgery, with classic pathological characteristics, such as capsular invasion, being seen in all eight patients. One subject (patient #1) had a suggestive history for hyperparathyroidism–jaw tumor syndrome, with a jaw tumor and a brother with benign PHPT. He was subsequently tested for *HRPT2* mutation and was found to be positive. Since commercial testing was not available at the time of study initiation, other patients were not routinely tested for *HRPT2*.

Eighteen subjects with benign PHPT were also enrolled. In the benign PHPT urinary control group, ten patients had measurement of urinary hCG and of the urinary ratio of the malignant hCG isoform. In the benign PHPT serum control group, eight other patients had measurement of the malignant hCG isoform in the serum. In both control groups, benign PHPT was characterized by asymptomatic mild hypercalcemia and elevated PTH levels. The benign PHPT patients were seen in our Bone Unit at the same time that the study data were being collected on the PtCa subjects. There was no known bias in terms of the way the PHPT subjects were selected. None had clinical features of PtCa, such as a palpable neck mass or significant renal or skeletal disease (1). The Institutional Review Board of Columbia University Medical Center approved the protocol. All patients gave written informed consent.

Protocol

Serial measurements of urinary and serum hCG were performed in the cancer patients at study entry and then at varying intervals after exposure to cinacalcet (administered on an escalating dosage regimen 30 mg twice daily to 90 mg four times daily) over 16 weeks. The 18 patients with benign parathyroid disease had a single measurement of hCG (ten of urine and eight of serum). The PHPT patients did not receive cinacalcet. All urine samples were measured in a first morning void and all blood samples were obtained fasting in the morning. In the cancer patients, samples were collected prior to the morning cinacalcet dose. Serum and urine were immediately frozen and kept at -80 degrees. Serum calcium and PTH measurements were made in all patients.

Biochemical determinations

Serum calcium was measured at Covance Laboratory (Indianapolis, IN, USA). Intact PTH was measured using an IRMA (coefficient of variation, CV = 4.2–6.4%; Allegro PTH, Nichols Institute Diagnostics; San Juan Capistrano, CA, USA).

The hCG measurement in urine was performed with two-site IRMAs measuring hyperglycosylated hCG (B152 capture), hCG, and β subunit (CTP104 capture) using a detection antibody directed to hCG and hCG β but not to the CTP region (B207). Monoclonal antibodies B152 and B207 have been described along with procedures for their use in two site immunometric assays (10,11). The hCG employed as standard for these assays was the new WHO 1st Reference Reagent for Immunoassay 99/688 (12). B207 was used as detection (radiolabeled antibody) and B152 as capture antibody for measuring hyperglycosylated (core 2) hCG (12), while CTP104 was used as capture antibody for measuring total hCG (core 1 and core 2 forms) (12,13). Capture antibodies B152 and CTP104 recognize epitopes on the CTP and are sensitive to the glycosylation status of this portion of hCG (13,14). The presence of hyperglycosylated hCG isoforms was detected by a ratio method that involved two sandwich immunoassay measurements on the same specimen using the hCG RP as standard. The amount determined in an assay using B152 for capture and ^{125}I -B207 for detection was divided by that measured in an assay using CTP104 for capture and ^{125}I -B207 for detection. The ratios found ranged between 0.5 and 4 with the highest ratio indicative of the highest content of B152 isoforms.

In serum, a direct analysis for hyperglycosylated hCG used an automatic assay system standardized with a hyperglycosylated hCG form isolated from a cancer patient (the immunogen for antibody B152) (15).

Statistical analysis

Statistical analyses were performed using SPSS (version 11). Continuous data are presented as mean value \pm S.D.; categorical data are reported as absolute number. A Cox proportional hazards model was used to estimate the survivor function as predicted by urinary hCG levels with four observed and four right-censored observations. The levels of urinary hCG for hypothetical patients with PtCa were entered into the resultant model to show the failure curves that would be predicted.

Results

Urinary hCG

The ten benign PHPT urinary control subjects (two males, eight females; age: 63 ± 15 years) had mildly elevated serum calcium (2.7 ± 0.1 mmol/l; nl: 2.1–2.6 mmol/l) and PTH (9.7 ± 0.2 pmol/l; nl: 1.0–6.8 pmol/l) levels, while the PtCa patients (five males, three females; age: 56 ± 13 years) had markedly elevated serum calcium (3.9 ± 0.5 mmol/l; $P < 0.0001$ versus benign

PHPT urinary controls) and PTH levels (81.1 ± 64 pmol/l; $P = 0.003$ versus benign PHPT urinary controls) at presentation (Table 1).

Total urinary hCG was normal in the benign PHPT urinary controls subjects (range: 0–17 fmol/mg Cr; $nl < 50$). In the subjects with PtCa, the initial hCG levels were measured at a mean of $9 \pm$ (range: 4–26) years after parathyroid carcinoma surgery (Figure 1). In these subjects, three of the eight patients (one male) had persistently normal total urinary hCG levels (< 50 fmol/mg Cr). These three subjects all survived without major complications in 2 years of follow-up.

Three of the other subjects with PtCa (one male) had persistently abnormal elevations in total urinary hCG (range: 217–1986 fmol/mg Cr). The three patients showed a trend towards higher serum calcium levels when compared with the three PtCa patients with normal hCG (3.3 ± 0.5 vs 3.0 ± 0.3 mmol/l). The three patients with elevated hCG all had a poor prognosis with hip fracture ($n = 3$) and death ($n = 2$) occurring within 3 and 6 months respectively of their highest hCG measurements.

In the two remaining cancer patients (both males), total urinary hCG became abnormally elevated over time. Again the presence of high hCG levels heralded a poor outcome. In one patient (patient #7), PTH increased, while in the other (patient #8), marked decreases in BMD (7.2% at the spine, 5.4% at the total hip, and 3.5% at the distal 1/3 radius) were observed over the interval in which hCG levels rose. This patient sustained a hip fracture within 4 months and both patients died within 10 months of the rise in hCG levels (Figure 2).

All of the five cancer patients with an elevated total urinary hCG had a high level of the urinary malignant hCG hyperglycosylated isoform. In contrast, this isoform was undetectable in the other three cancer patients with the better clinical outcomes and in the benign PHPT subjects.

Serum hCG

The benign PHPT serum control subjects (three males, five females; age: 62 ± 13) had mildly elevated serum calcium (2.7 ± 0.2 mmol/l; $P < 0.0001$ versus cancer subjects) and PTH (12.3 ± 6.2 pmol/l; $P = 0.009$ versus cancer subjects) levels. In the serum, only the malignant isoform, and not total serum hCG, was measured. The normal range for serum malignant hCG is not defined. In the benign PHPT subjects, the range of serum malignant hCG was 1.76–3.77 pmol/l. The cancer patients tended to have higher serum malignant hCG values than the PHPT patients, ranging from 2.01–10.81 pmol/l. Although values below 3.77 pmol/l (the maximum value in a PHPT subject) were observed in the cancer patients, all of the cancer patients had serum malignant hCG values that exceeded that maximal PHPT value at least at one of the serial time points.

Effects of cinacalcet

The hCG levels were obtained at varying time points of cinacalcet administration (range of time points: 0–120 weeks). Nevertheless, there did not appear to be an effect of cinacalcet on the hCG levels.

Discussion

We found that the hCG levels were elevated at certain time points in most patients with PtCa. The malignant isoform of hCG, the predominant form in these patients, was not seen at all in subjects with PHPT. In patients with malignant disease, increased urinary hCG or a rise in urinary hCG levels appeared to signal a more aggressive stage of PtCa. High urinary hCG levels were associated with a greater likelihood of hip fracture and death. Hip fractures and/or death occurred in the five cancer subjects with persistently high or rising hCG levels, while neither occurred in the three cancer subjects with persistently low hCG levels.

These data suggest that the urinary hCG levels might have the potential to discriminate between parathyroid adenomas and carcinomas. In our pilot sample, the sensitivity was ~40% (three of eight patients with carcinomas had raised urinary hCG), but the specificity was 100% (none of the ten urinary measurements done in PHPT were above the diagnostic threshold). Future studies with larger numbers of subjects would help to better define the properties of urinary hCG as a diagnostic test in parathyroid carcinoma. Even if the sensitivity in a larger population were found to be no higher than 50%, the negative predictive value (the probability that a cancer-free subject will test negative) would still be high because of the very low prevalence of parathyroid carcinoma. In other words, a normal urinary hCG at diagnosis does not rule out the possibility of PtCa, but an elevated urinary hCG confirms it.

hCG is well-known to be expressed in gestational trophoblastic disease and in germ cell tumors (7). However, it can be expressed by nontrophoblastic cancers as well. These include transitional cell carcinoma of the bladder and urinary tract (16), renal cancer (17), prostate cancer (18), gastrointestinal cancer (19), carcinoid (20), lung cancer (21), breast cancer (22), gynecologic cancer (23), oral cancer (24), and lymphoma (25). In general, hCG is more likely to be expressed when these tumors are poorly differentiated. β hCG appears to enhance the growth of tumor cells in culture by preventing apoptosis (26), possibly explaining why the expression of β hCG is associated with aggressive cancer. Hyperglycosylated hCG, the malignancy-associated isoform, is the predominant isoform of hCG in a healthy pregnant woman until the 6th week of gestation (11,14). It is also produced in choriocarcinomas and can be detected by an antibody that was raised using a choriocarcinoma-derived form of hCG (10). The concentration of hyperglycosylated hCG has been shown to correlate with malignancy (8).

In a previous study, Stock and colleagues measured the concentration of hCG subunits in the serum of 70 patients with PHPT, 3 of whom had PtCa (27). Two of the cancer patients had elevations in α - and β -hCG, which fell after surgical cure. In the same study, selective venous catheterization in 42 patients with benign PHPT yielded tenfold gradients of PTH, as expected, but also a mild elevation of hCG α -subunit in one patient (27). In another report, immunostaining of parathyroid tissue was positive for hCG in 6 out of 31 patients with parathyroid adenomas and in 1 out of 3 cancer patients (28). These immunohistochemical data suggest that parathyroid cells can acquire the capacity to synthesize and express hCG.

Cinacalcet did not appear to affect hCG levels, although a limitation of this study is that the hCG levels were obtained at varying time points of cinacalcet administration. Cinacalcet has been shown to lower serum calcium levels in PtCa (29), but its effect on the progression of the underlying disease is unknown. An additional limitation is the small number of PHPT subjects; it is conceivable that evaluation of additional PHPT subjects might have revealed elevated hCG levels in some patients with benign disease. A larger study with more PHPT subjects would be able to extend our preliminary observations.

In conclusion, this brief report calls attention to the need for a more detailed investigation of hCG in malignant and benign parathyroid disease. A future area of investigation would be immunolocalization of hCG in the histological samples of the cancers themselves, a finding that would confirm that PtCa is indeed the source of the hCG measured in serum and urine. These early results suggest that hCG might have the potential to become a marker of disease progression in malignant parathyroid disease. Investigation of patients who have clinically and biochemically severe, but pathologically benign, parathyroid disease and those with malignant pathology, despite mild clinical features, will help to elucidate further the utility of hCG as a marker for parathyroid carcinoma.

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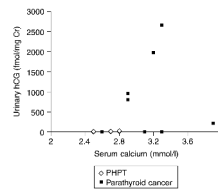


Figure 1.

The distribution of urinary hCG values in PHPT and parathyroid carcinoma subjects. A normal urinary hCG does not rule out the possibility of parathyroid cancer (sensitivity is low), but an elevated urinary hCG confirms it (specificity is high).

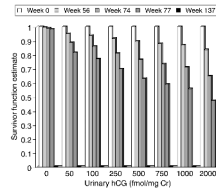


Figure 2.

The survivor function predicted from the Cox proportional hazards model estimated from the study observations. The survivor function estimate was applied to urinary hCG measurements of 0, 50, 100, 250, 500, 750, 1000, or 2000 fmol/mg Cr at weeks 0, 56, 74, 77, and 137. Increasing urinary hCG measurements are associated with a decreasing survivor function.

Table 1

Individual urinary human chorionic gonadotropin (hCG) levels (total levels and ratio of malignant hCG:total hCG), calcium, parathyroid hormone (PTH), and clinical outcomes for ten primary hyperparathyroidism (PHPT) subjects and eight parathyroid carcinoma subjects.

Subjects	Urinary hCG fmol/mg Cr nl:< 50	Urinary malignant isoform nl: <0.5	Calcium nl: 2.1–2.6 mmol/l	PTH nl: 1.0–6.8 pmol/l	Hip fracture/ death
PHPT subjects (n = 10)	6.1 ± 6	0	2.7 ± 0.1	9.7 ± 0.2	No/No
Parathyroid carcinoma subjects (n = 8)					
Persistently low hCG (n = 3)	1 0	0	2.6	118	No/No
	2 0	0	3.1	18.2	No/No
	3 3	0	3.3	35	No/No
Persistently high hCG (n = 3)	4 800	0.9	2.9	128	Yes/Yes
	5 1986	0.8	3.2	87	Yes/Yes
	6 217	0.6	3.9	54	Yes/No
Rise in hCG (n = 2)	7 0	0	3.2	36	No/Yes
	2662	1.7	3.3	130	
	8 0	0	3.8	222	
	956	1.5	2.9	227	Yes/Yes

Carcinoma subjects are grouped according to whether their hCG levels were persistently low, high, or increased over time. The values in the cancer subjects were those obtained at initial hCG measurement, which were measured at varying stages of cinacalcet treatment. Repeat hCG levels are shown for subjects 7 and 8; the levels remained unchanged in the first six subjects. Values are mean ± S.D.