Clinica Chimica Acta 438 (2015) 181–185

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

Case report

Discrepant serum and urine β-hCG results due to production of β-hCG by a cribriform-morular variant of thyroid papillary carcinoma

Mir Alikhan [a], Anoopa Koshy [b], Elizabeth Hyjek [a], Kerstin Stenson [c], Ronald N. Cohen [b,1], Kiang-Teck J. Yeo [a,*,1]

[a] Department of Pathology, Biological Sciences Division, The University of Chicago, 5841 S. Maryland Avenue, Chicago, IL 60637, United States
[b] Section of Endocrinology, Department of Medicine, Biological Sciences Division, The University of Chicago, 5841 S. Maryland Avenue, Chicago, IL 60637, United States
[c] Department of Surgery, Biological Sciences Division, The University of Chicago, 5841 S. Maryland Avenue, Chicago, IL 60637, United States

ARTICLE INFO

Article history:
Received 11 July 2014
Received in revised form 21 August 2014
Accepted 22 August 2014
Available online 30 August 2014

Keywords:
Human chorionic gonadotrophin
Thyroid papillary cancer
hCG immunoassays

ABSTRACT

Background: Although patients with medullary thyroid cancer are known to present with paraneoplastic hormone production, this is much less common with papillary thyroid cancer.
Methods: We present a patient with the cribriform morular variant of papillary thyroid cancer in association with familial adenomatous polyposis who developed a positive pregnancy test in the absence of known pregnancy. The patient had developed vaginal bleeding, and her laboratory testing was characterized by elevated serum human chorionic gonadotropin (β-hCG) concentrations, but negative qualitative urine results. After a thorough gynecological evaluation to exclude unexpected normal, ectopic, or molar pregnancy, we pursued an evaluation for other sources of β-hCG production.
Results: We showed that the elevated serum β-hCG concentrations were not the result of heterophile antibody interferences, and ultimately we proved that her recurrent tumor produced the ectopic β-hCG. This is the first report of β-hCG production by papillary thyroid cancer. Thus, the possibility of ectopic production of β-hCG by papillary thyroid cancer needs to be included in the differential diagnosis of elevated hCG concentration in the absence of pregnancy.
Conclusions: This study of an unusual paraneoplastic syndrome highlights the importance of investigating discrepancies in the clinical laboratory.

1. Introduction

Human chorionic gonadotropin (hCG) is a 37 kDa glycoprotein primarily secreted by the fetal placenta following conception and implantation [1]. It functions to stimulate progesterone secretion by the corpus luteum during the first weeks of pregnancy, which promotes the viability of the fetus largely through thickening and maintenance of the uterine lining, providing adequate nourishment for the developing conceptus. Thereafter, concentrations of hCG decline as the placenta begins production of progesterone and estrogen [2]. hCG is also thought to have an immunosuppressant function [3], reducing the likelihood of fetal rejection by the maternal immune system.

The hCG molecule is composed of 244 amino acids and consists of a heterodimer with an α and β subunit. The alpha subunit is identical among the glycoprotein hormones, namely LH, FSH, and TSH. The β subunit, however, is unique to the hCG molecule. It is the targeting of antibodies against various epitopes of the β subunit that confers relative specificity for laboratory hCG testing, and this methodology is employed by most modern clinical chemistry assays [4].

The main physiologic role of hCG is within the context of normal pregnancy. As a result, increased hCG concentrations are essentially diagnostic of pregnancy; hCG testing can quickly and effectively rule in or rule out pregnancy in the appropriate clinical context. Recent development of point-of-care (POC) devices for its measurement in urine has provided rapid, simple methods for the detection of pregnancy, with sensitivities approaching that of serum in conventional laboratory analyzers [5].

Elevated hCG concentrations are most often due to pregnancy, whether intra-uterine or ectopic. However, the specificity is not perfect due to the uncommon occurrence of elevated concentrations seen in disease states, both benign and malignant. Rarely, the pituitary gland may secrete hCG in perimenopausal women due to release of negative feedback on gonadotropin releasing hormone (GnRH) secretion [6]. Gestational trophoblastic diseases (GTDs) are rare and comprise a spectrum of both benign (hydatidiform moles) and malignant (invasive moles, choriocarcinomas, placental site trophoblastic tumor, and epithelioid trophoblastic tumor) disorders. Each is characterized by the production by the lesional trophoblast of abnormally high concentrations of β-hCG [7]. Rarely, a non-pregnant woman with a history of

* Corresponding author at: 5841 S. Maryland Ave., MC 0004, TW-010, Chicago, IL 60637, United States.
E-mail address: jyeo@bsd.uchicago.edu (K.-T.J. Yeo).
[1] Co-senior authors.

http://dx.doi.org/10.1016/j.cca.2014.08.026
0009-8981/

gestational trophoblastic disease may have persistent low concentrations of hCG following treatment, termed "quiescent GTD." [8].

An exceptionally rare cause of elevated hCG in a non-pregnant female is due to paraneoplastic secretion of the hormone by extraplacental tissues. Such cases have been reported in various neoplasms [9–14]. Paraneoplastic syndromes associated with thyroid carcinoma are rare, and hCG secretion has never been reported in association with this neoplasm. The present patient with papillary thyroid carcinoma (PTC) and subsequent vaginal bleeding had elevated plasma β-hCG concentrations due to secretion by her thyroid neoplasm.

2. Patient

The patient is a 31-y-old woman with a history of Gardner syndrome (familial adenomatous polyposis; FAP). Due to her family history of colon cancer, she underwent colonoscopy at age 20 y and on biopsy, had multiple colonic tubular adenomas. She underwent total colectomy at the age of 22 y. She also developed a retroperitoneal desmoid tumor requiring surgical excision and repeated placement of ureteral stents due to hydronephrosis. The patient first presented to the Endocrinology Clinic at the University of Chicago at the age of 25 y for goiter. Physical exam revealed bilateral thyroid nodules. She was clinically euthyroid, and a TSH was 0.9 mIU/l (reference range, 0.3–3.8 mIU/l) with free thyroxine index (FTI) of 8.1 (reference range, 6.0–10.5). A thyroid ultrasound confirmed multiple bilateral thyroid nodules. Fine needle aspiration of two of these nodules was consistent with papillary thyroid carcinoma. She underwent a total thyroidectomy, which revealed multifocal papillary thyroid carcinoma (cribriform-morular variant), that extended to the inked margins of the surgical specimen. No nodes with metastatic carcinoma were identified. After surgery, she was treated with 30 mCi ^{131}I (TSH was 130 mIU/l, and a thyroglobulin concentration was 3.0 ng/ml with negative anti-thyroglobulin antibodies); a post-therapy scan showed uptake only in the thyroid bed.

She was lost to follow-up for about a year. When she returned back to clinic, her TSH was 0.7 mIU/l with a thyroglobulin of 2.0 ng/ml. On physical exam, multiple abnormal masses in her neck were identified. Fine needle aspiration of these lesions was consistent with recurrent carcinoma. She underwent neck dissection, and the pathology showed metastatic cribriform-morular variant (C-MV) of papillary thyroid carcinoma was present in the lymph nodes and neck musculature. She was taken off levothyroxine after surgery and her TSH increased to 170 mIU/l with a thyroglobulin concentration of <1.0 ng/ml. A dose of 100 mCi ^{131}I was given, and a post-therapy scan was negative for metastatic disease.

She developed persistent macroscopic disease on cross-sectional imaging that increased in size. She declined further surgery at that time, as well as consideration of external beam radiation therapy. Over the next few years, she tried various alternative treatment strategies, and took her levothyroxine dose only intermittently. She returned to the Endocrine Clinic at age 29 y with large, bulky neck masses, a left pleural effusion, and pleural-based masses. The pleural fluid was drained, and cytology was consistent with reactive mesothelial cells. The patient continued to refuse radiation or consider chemotherapy, and preferred to experiment with alternative therapies. Her neck masses continued to grow and eventually broke through the overlying skin. A surgical debulking procedure was planned. She was seen at another institution for a second opinion and was scheduled for an MRI of the neck. A serum pregnancy test at this institution was positive and the MRI was canceled. The patient also recalled a recent episode of abnormal vaginal bleeding. She was subsequently seen at the Ob-Gyn clinic at the University of Chicago for further evaluation. A urine pregnancy test was negative. The patient was then referred to a family planning center for IUD placement; a plasma pregnancy test there was again positive. She was then referred back to the University of Chicago for further evaluation.

The clinical chemistry laboratory was consulted to address the apparent discrepancy between the urine and plasma hCG tests, as the sensitivity of the POC device is comparable with that of laboratory analyzers. This was resolved by a series of studies. First, a linearity study was set up to assess parallelism with serial dilutions of the patient's samples. Frozen serum samples received two and six months previously for thyroglobulin testing from the same patient were retrieved and also tested for β-hCG concentration as part of this study. The results demonstrated excellent parallelism in all samples, indicating good recovery for β-hCG (data not shown).

The possibility of a falsely positive plasma β-hCG was considered due to heterophile antibodies - endogenous human anti-animal antibodies that may interfere non-specifically with immunometric assays by cross-linking the signal and capture antibodies [15,16]. The detection of heterophile antibodies in the context of hCG testing may be undertaken using three different approaches. The first employs the concept that heterophile antibodies are too large to be excreted in urine. Thus, a urine test for hCG would help confirm if the plasma test was truly positive. In our case, this was considered a possibility, but further testing of this patient's plasma on the QuickVue hCG POC device used in urine testing showed a negative hCG reading even though the quantitative value was ~160 mIU/l by an alternate hCG method. (A male control plasma showed negative reading while a pregnant female patient of hCG of 166 mIU/l showed a positive reading with the POC device). Additionally, a mixing study was carried out, where control pregnant patient plasma at a predetermined concentration of 437 mIU/l was added as an equal parts mixture to this patient plasma, yielding a β-hCG of 282 mIU/l. When both the undiluted control and the equal parts mixture were tested on the QuickVue POC device, they gave a positive result, while the patient's undiluted plasma was negative. This verified that no endogenous interfering substances were present in the patient's plasma that could be interfering with the assay.

A second approach is to measure the plasma sample by different quantitative hCG assays, since it is unlikely that all of them will show the same false positive results due to interference by heterophile antibodies. In our case patient, an hCG of 139 mIU/ml was obtained with the Elecsys total hCG, while <0.5 mIU/ml was obtained using the Elecsys intact hCG assay. Thus the calculated "free β-hCG", (defined as total hCG-intact hCG) constitutes the predominant form of hCG in our patient. Another total hCG assay (Beckman Access) showed a similar value of ~129 mIU/ml, while various other commercial hCG assays yielded values of 50–346 mIU/ml (Table 1).

A third, more specific approach, however, is the use of heterophile antibodies blocking agents (Scantibodies Laboratory). These are nonimmune, animal immunoglobins that are able to block heterophile antibodies in patient serum, preventing them from binding reagents antibodies in the assay. In our case, the addition of the blocking agents, however, did not appreciably affect the hCG results suggesting that heterophile antibodies were unlikely present to interfere with the hCG assay. Taken together, these results strongly suggest that the positive plasma hCG detected in this patient represents true, circulating hCG in this patient.

Within the next couple of weeks, the patient agreed to undergo a surgical debulking procedure as palliative therapy to reduce tumor burden in her neck. The resected specimen was received by surgical pathology (Fig. 1A) and showed a 16 cm mass with tumor erupting through the overlying skin. The otherwise white-tan skin showed foci of hemorrhage and discoloration overlying the tumor. Serial sectioning of the tumor demonstrated an infiltrative, solid, heterogeneous cut surface with gross infiltration into fat and skeletal muscle and involvement of surgical margins (Fig. 1B). Microscopy of the tumor showed histology similar to the patient's previous thyroidectomy and resection specimens. More specifically, the lesion was composed of sheets and nests of malignant cells (Fig. 1C) with increased nucleus to cytoplasm ratio, elongated, grooved nuclei, and prominent nucleoli, indicative of PTC. Areas of cribriform architecture were identified (Fig. 1D) as well as