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CASE REPORT

Documentation of Complete Resolution of Gestational Choriocarcinoma in the Oophorectomized Patient

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A 39-year-old woman with choriocarcinoma metastatic to the lungs and parametrium underwent total abdominal hysterectomy/bilateral salpingo-oophorectomy and follow-up chemotherapy with regression of the hCG assay, plateauing at 9 mIU/ml. Spinal fluid hCG assay was negative. An LH assay was performed which was 135 mIU/ml (2nd IRP-HMG). A quantitative hCG assay was performed on two sources of purified LH at varying concentrations to determine the contribution of LH cross-reactivity. When corrected for the LH contribution, the quantitative hCG was zero. Chemotherapy was discontinued. At 12-months follow-up the patient has remained in complete chemical remission and has an excellent performance status. Whenever a patient is oophorectomized, LH cross-reactivity should be ruled out as a cause for persistent low titers of hCG.

INTRODUCTION

Gestational trophoblastic neoplasia is the first solid tumor which demonstrated a complete response to chemotherapy [1]. Even in the presence of metastatic disease to the lungs, a complete response can be obtained in nearly 100% of the patients [2]. The mainstay of treatment remains chemotherapy, however hysterectomy has been performed in women who desire sterilization, as primary management of nonmetastatic trophoblastic disease and for uterine disease resistant to chemotherapy [3]. The documentation of disease regression is provided by serial quantitative serum hCG assay. Persistent disease has been described when the serum hCG values rise for 2 weeks or plateau for 3 weeks or more.

We describe a patient whose serum hCG assay plateaued at a low level who ultimately proved to have complete disease regression.

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CASE HISTORY

A 38-year-old Vietnamese female, G5 P3, with last menstrual period 10 weeks prior to admission was referred to the Stanford University faculty practice in gynecologic oncology with a quantitative hCG assay at 1.2 million mIU/ml. She reported scant vaginal spotting over the last few weeks but no passage of tissue or vesicles, and a weight loss of 9.0 kg from her usual 51.0 kg. She also complained of difficulty breathing but had no history of palpitation or hemoptysis. Past medical history was significant in that her first pregnancy ended in a molar gestation at 20 weeks in 1976. She subsequently had three normal-term vaginal deliveries.

Physical examination revealed a cachectic, anxious woman with a heart rate of 120 beats per minute. The blood pressure was 110/80. There was no orthostatic hypotension. The lungs were clear to bilateral auscultation. The abdominal examination revealed no mass, no hepatosplenomegaly, and no tenderness. Pelvic examination revealed a 5-cm adnexal mass which was contiguous with the uterus which enlarged to 12-week size. An endometrial biopsy was performed which revealed no evidence of carcinoma.

The patient was admitted to Stanford University Hospital for further investigation and treatment. Peripheral hyperalimentation was initiated because the patient was anorectic and had an absolute lymphocyte count of less than 1000/dl. Laboratory studies revealed a hematocrit of 38.3, a free T-4 of 20.8 ng/dl, and a free T-4 index of 10. The SGPT was 65 IU/liter and alkaline phosphatase

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was 146 IU/liter. The remainder of the chemistry and electrolyte panel was normal. An endocrinology consultation was obtained to assist in the management of the thyrotoxicosis. The patient received intravenous Inderal titrated up to doses of 8.0 mg every 6 hr in order to bring the heart rate down to 80–90. The patient was also prescribed potassium iodide (SSKI), 4 drops every 6 hr and propothiouracil (PTU), 200 mg by mouth, three times daily.

Posteroanterior and lateral chest X-rays of the lungs showed multiple bilateral 1- to 2-cm pulmonary nodules in the left lower and right midlung fields. No pleural effusion was present. A CAT scan of the brain with contrast using 1.0-cm cuts was negative. CAT scan of the abdomen and pelvis showed the inferior-most lung lesions to be 2 cm in maximum diameter, and revealed that the liver, spleen, pancreas, adrenals, and kidneys were normal. There was no retroperitoneal adenopathy and no intra-abdominal or pelvic fluid. Within the pelvis, however, bilateral complex cystic and solid adnexal masses were demonstrated. The left adnexal mass contained a large soft tissue component and measured 5.5 × 7.0 cm compressing the wall of the bladder and extending inferiorly to the left lateral fornix of the vagina. The right-sided, predominantly cystic mass measured 3 × 3 cm. The uterus was not well delineated but appeared to be somewhat enlarged. The final impression by CAT scan was that the left ovary was consistent with metastatic choriocarcinoma and the right ovary with thecalutein cysts. An MRI was performed for added detail. This revealed a single large inhomogeneous pelvic mass that appeared to invade the uterus, measuring 11 × 9 × 10 cm, displacing the uterus anteriorly and invading it along the posterior margin. Neither adnexa could be identified by MRI. An endovaginal ultrasound revealed an empty uterus and a greatly enlarged vascular stroma and myometrium with slightly enlarged but normal ovaries. The tentative diagnosis was metastatic choriocarcinoma in the pelvis. A lengthy discussion was undertaken with the patient who stated that she desired sterilization.

Exploratory laparotomy revealed a diffusely enlarged uterus with large, solid, serpiginous, apparently intravascular tumor metastasis in the bilateral parametrial regions. The uterus and bilateral ovaries weighed 270 g. The uterus itself contained dense vascular metastasis of choriocarcinoma throughout the full thickness of the myometrium of the fundus and isthmus. The left paracervical region had invasive choriocarcinoma resected with negative margins. The endometrium revealed a progestational effect. Both fallopian tubes and ovaries were normal. The right mesovarium contained vascular metastasis of choriocarcinoma as did the infundibulopelvic vein and ligament.

Postoperatively, the patient's thyroid status remained stable on gradually decreasing doses of intravenous Inderal. Hyperalimentation, which had been initiated preoperatively in order to minimize postoperative risk to wound healing, was continued. She began taking oral liquids on Postoperative Day 4 and regular diet the next day. Postoperative serum quantitative hCG of 50,243 mIU/ml.

Chemotherapy was initiated consisting of etoposide, methotrexate, and actinomycin D (EMA) [4]. The patient tolerated the chemotherapy very well. The heart rate had remained stable at 80–90 beats per minute on 40 mg of oral Inderal. The patient was discharged on Inderal, PTU, SSKI, and compazine. She returned 1 week later for vincristine and cyclophosphamide intravenous chemotherapy (CO) and received weekly alternating EMA–CO for eight courses. By Postoperative Week 14, the quantitative hCG had regressed to 9 mIU/ml and then began to plateau for 3 weeks (Fig. 1). Physical exam with detailed neurologic exam was entirely normal. A lumbar puncture was performed for cerebrospinal fluid hCG assay which was negative. Etoposide with cisplatin was then initiated.

A quantitative LH (Amerlex-M LH RIA, Amersham Corporation, now Eastman Kodak Company, Rochester, NY) was performed on serum obtained from the patient which revealed 135 mIU/ml (2nd IRP–HMG) with hCG of 8 mIU/ml (2nd IS). One week later, a repeat assay revealed an LH of 186 mIU/ml and an hCG of 5 mIU/ml. Although the instruction manual of Amerlex-M βhCG RIA kit has indicated a 1.6% cross-reactivity of LH, an interference of LH to the hCG assay was evaluated. The purified LH from two sources, (A) Pacific Biotech, Inc. (San Diego, CA) and (B), the National Institute of Arthritis, Metabolism, and Digestive Disease (hLH-I-1, AFP-4345B), were assayed with Amerlex-M LH RIA to determine the potencies of LH in mIU/ml (2nd IRP–HMG). LH from the two sources of A and B were diluted serially and their hCG activities are determined with the Amerlex-M βhCG RIA kit. The result is shown in Fig. 2, from which the cross-activities of LH are calculated to be 2.4 and 1.7% from sources A and B, respectively. Percentage cross-reactivity is expressed in a conventional way as the ratio of hCG concentration to LH concentration which results in a 50% inhibition of maximal binding (B/B_0) [5]. As indicated in Fig. 2, however, the dose inhibition curves were not parallel. LH at the low level (<200 mIU/ml) exhibit hCG activity which is significant enough to disturb the decision making in clinical management. Table 1 demonstrated the contribution of LH cross-reactivity to hCG assay. It becomes clear that at certain physiological conditions such as ovulation or postmenopause the concentration of serum LH interferes with the Amerlex-M βhCG assay. From this it was determined that the patient's persistently elevated hCG was clearly due to LH cross-reactivity. Oral 17β-estradiol was pre-

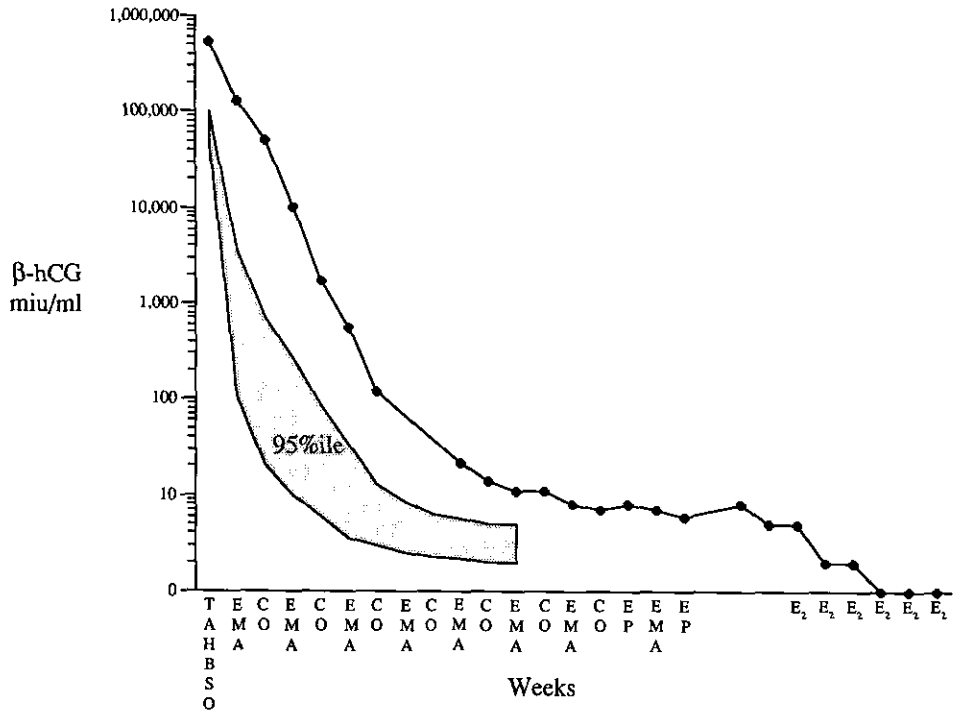

FIG. 1. Log graph of weekly βhCG concentration (TAHBSO, total abdominal hysterectomy and bilateral salpingo-oophorectomy); EMA, etoposide, methotrexate, and actinomycin D; CO,-cyclophosphamide and Oncovin; EP, etoposide and cisplatin; E_2, conjugated estrogens.

scribed for the patient. Three weeks later, a quantitative hCG was negative. Chemotherapy was discontinued. One year after completion of chemotherapy the patient has remained in both chemical as well as physical remission.

DISCUSSION

The observation of confounding effects of an elevated LH on βhCG assessment in a castrated woman after treatment for gestational trophoblastic neoplasia is not new [6]. This phenomenon should be suspected even in trophoblastic disease cases when oophorectomy has not been performed because many chemotherapy agents useful in treating persistent trophoblastic disease, especially alkylating agents such as cyclophosphamide and chlorambucil, can cause permanent crosslinks, breaks, and omissions in the DNA strand, resulting in ovarian failure.

A purely clinical method of detecting the presence of pituitary LH in the serum would entail prescribing adequate hormone replacement therapy to suppress LH secretion and then measuring serum βhCG again. However, it is sometimes important to know promptly what proportion of an elevated hCG titer comes from pituitary

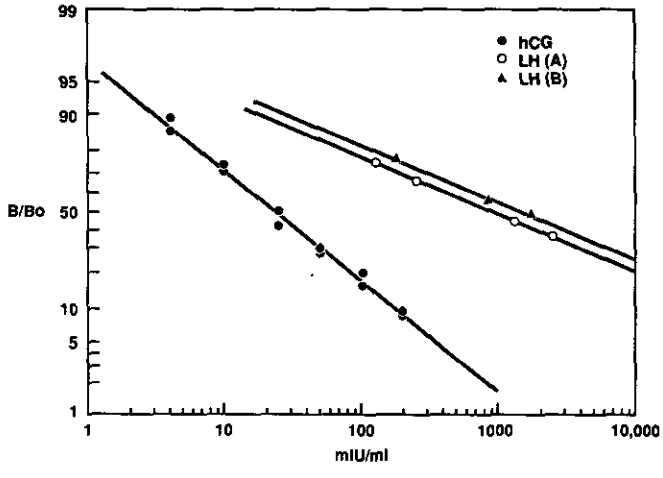

FIG. 2. Cross-reactivity of LH to Amerlex-M βhCG assay.

TABLE 1
Contribution of LH to hCG Assay (Amerlex-M βhCG RIA)

	LH (mIU/ml)	hCG observed (mIU/ml)	Interference[a] (%)
Source A	132	8	6.1
	264	12	4.5
	1320	27	4.5
	2640	39	1.5
Source B	87	0	0
	172	8	4.7
	869	20	2.3
	1719	26	1.5

[a] Interference, concentration of hCG/concentration of LH.

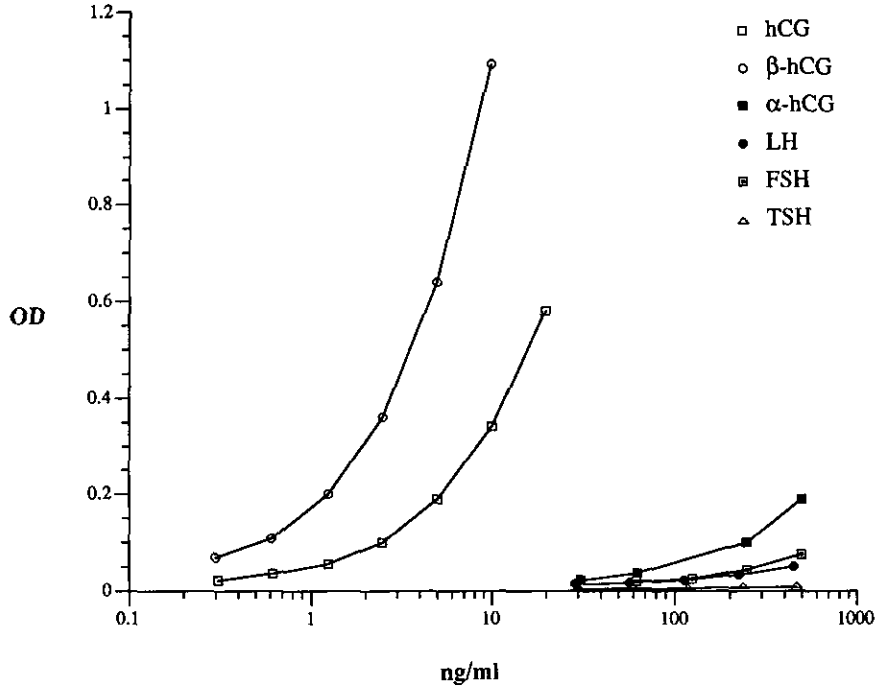

FIG 3. Cross-reactivities of gonadotropins to ES-300 hCG assay.

LH secretion. With frozen sera from previous assays, a quick determination of LH contribution can be obtained. A prolonged clinical approach could potentially delay much-needed salvage chemotherapy.

The human chorionic gonadotrophin is a glycoprotein which consists of two nonconvalently linked subunits. The α-subunits of all glycoprotein hormones are virtually identical and are composed of 92 amino acids. The β-subunits are made of 145 amino acids and are individual to each of the glycoprotein molecules. The immunoactivity of radioimmunoassays is specifically directed to the molecular differences of the individual β-subunits. The β-subunit of human chorionic gonadotrophin differs from that of LH only by the 30 terminal amino acids. The two protein hormones have similar function in that both support the corpus luteum, with rising levels of hCG during early pregnancy taking over after LH secretion decreases, approximately 8 days after ovulation.

The evolution of techniques to measure hCG started with the nonsensitive and nonspecific bioassay, followed by hemagglutination inhibition and latex agglutination inhibition and is currently performed by radioimmunoassay, enzyme immunoassay, and automated immunoassay. With the use of an antiserum generated against only the β-subunit of hCG, an hCG immunoassay can selectively measure hCG in samples that contain both LH and hCG. The advent of monoclonal antibody revolutionized the immunodiagnostic technology. Monoclonal antibodies appear to be superior to polyclonal antibodies with regard to homogeneity, specificity, and availability. However, it is well known that in addition to various glycosylated hCG molecules, a small amount of free α- and free β-subunits are secreted by trophoblast tissues. Cole and his colleagues [7–10] have demonstrated that nicked hCG (missing peptide linkage at β 44–45, or β 47–48), hCG missing the β-subunit c-terminal segment, and β-core fragment were also present in serum, urine, and reference standards. It is apparent that when multiple forms of hCG exist in the clinical specimens, polyclonal antibodies may be a better choice for the hCG immunoassay. In 1983, these same authors demonstrated that a radioimmunoassay employing only monoclonal antibodies did not offer any advantage over the radioimmunoassay that uses polyclonal antibodies [11].

Amerlex-M βhCG RIA employs an antiserum which is a polyclonal antibody generated against β-subunit hCG and has 1.6% cross-reactivity for LH by conventional definition. Our experience, however, indicated that at LH concentration of 130 mIU/ml, the cross-reactivity was 6% which contributed as much as 8 mIU/ml to the measured hCG. LH cross-reactivity should be suspected in any woman who has undergone bilateral oophorectomy who demonstrates persistent low levels of hCG, particularly when the assay is performed by conventional polyclonal radioimmunoassay. When LH cross-reactivity is suspected, a titration of this effect can be performed to

estimate the contribution of the LH molecule to the hCG assay and oral hormone replacement initiated to confirm this effect and obtain proof of chemical remission.

The result of immunoassay is greatly affected by the reference standard, specificity of antibody, matrix, methodology, and multiple species of antigen (ligand) in the specimen. Due to the multiple forms of hCG which existed in the clinical specimen, the hCG detection method of choice is a method using highly specific polyclonal antibody without nonspecific binding interference and matrix effect. The authors have not found a single perfect commercial available system yet. Currently, we use the automated immunoassay system, ES300 (Borehringer Mannheim Corporation, Indianapolis, IN) to determine hCG concentrations in patients. The antisera of hCG assay in ES300 are a combination of sheep polyclonal and murine monoclonal antibodies, which virtually eliminate any cross-reactivities from gonadotropins (see Fig. 3).

We also use Tandem-R hCG (Hybritech Inc., San Diego, CA) for pregnancy testing which can be modified to run the quantitative hCG assay. Tandem-R hCG is a solid phase, two-site sandwich-type immunoradiometric assay. It employs murine monoclonal antibodies and measures the whole molecule of hCG only. This method is used occasionally as a reference check for hCG results in question for the contribution of the β-subunit of hCG and other possible interference substances.

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