

**$\beta$ -hCG vs Intact hCG Assays in the Detection of Trophoblastic Disease**

Alan D. Rinker and Norbert W. Tietz

We describe a case of choriocarcinoma in which increased concentrations of  $\beta$ -choriogonadotropin subunits in serum indicated recurrence of metastasis long before the tumor could be confirmed by visualization techniques, while intact choriogonadotropin remained normal (<5 int. units/L). Therefore, detection or monitoring of choriocarcinoma requires the assay of free  $\beta$ -hCG subunit or an assay that measures both the free  $\beta$ -subunit and intact choriogonadotropin.

Trophoblastic disease is associated with an increase in intact (whole-molecule) choriogonadotropin (hCG) and free  $\beta$ -hCG subunits.<sup>1</sup> The mean ratio of free  $\beta$ -hCG to hCG is highest in choriocarcinoma (mean = 18.6) and lowest in hydatidiform mole (mean = 8.8). The ratio in choriocarcinoma has been reported to be as high as 91 (1); a high ratio is predictive of high-risk disease, requiring multi-agent chemotherapy (2). Therefore, detection or monitoring of trophoblastic disease requires the use of a free  $\beta$ -hCG subunit assay (1) or at least an assay that measures both the free  $\beta$ -subunit and intact hCG. The same also applies to the detection of testicular and some gastrointestinal tumors, which may secrete only free  $\beta$ -hCG subunits (3, 4). Tumors elaborating free  $\alpha$ -chains of hCG have also been reported (5).

Some widely accepted immunochemical hCG assays measure only the intact molecule and not the free  $\beta$ -subunit. These assays, when used alone, are not suitable for detecting or monitoring trophoblastic disease and some other types of tumors.

We report here the  $\beta$ -hCG and intact hCG results obtained for a patient with choriocarcinoma and multiple metastases to the brain and lungs. Detailed information on the clinical course and treatment of the patient are reported elsewhere (6). Highlights are summarized in Table 1.

**Materials and Methods**

The  $\beta$ -hCG assay was carried out with the Tandem-R hCG test kit (Hybritech, Inc., San Diego, CA 92121), which detects both free  $\beta$ -hCG subunits and intact hCG. The intact hCG assay was performed with a fluorometric enzyme immunoassay (Stratus hCG; American Dade, Miami, FL 33152), which detects only the intact hCG molecule. Both procedures are standardized against the World Health Organization's 1st International Reference Preparation (IRP no. 75/537).

**Results**

The patient was a 30-year-old woman with a nine-month history of amenorrhea and a  $\beta$ -hCG value on admission of 3800 int. units/L. Results of neurological and physical

Division of Clinical Chemistry, Department of Pathology, University of Kentucky Medical Center, Lexington, KY 40536.

<sup>1</sup> Nonstandard abbreviations: hCG, human choriogonadotropin; EMA, Course A, consisting of etoposide, dactinomycin, and methotrexate (Day 1) and etoposide, dactinomycin, and folinic acid (Day 2); and CO, Course B, consisting of vincristine and cyclophosphamide.

Received April 18, 1989; accepted May 15, 1989.

**Table 1. Correlation of Selected  $\beta$ -hCG and hCG Values with Treatment Regimen**

Date	$\beta$ -hCG	Intact hCG	Treatment regimen
	Int. units/L		
4-18-86	3800		Admission; lesions found in brain and left lower lobe of lung
4-22-86	6200		Radiation therapy started
5-05-86	7600		Completion of first course of modified Bagshawe chemotherapy
5-11-86	890		Second course of chemotherapy
5-19-86	138		
6-16-86	5.4		Third course of chemotherapy
7-18-86	<5.0		Fourth course of chemotherapy
10-24-86	8.1	<5.0*	Possible recurrence of metastatic gestational trophoblastic disease
10-31-86	14	<5.0	Fifth course of chemotherapy
12-13-86	15	—	Hysterectomy on 12-8-86; no evidence of trophoblastic disease in tissue removed
1-20-87	14	—	Sixth course of chemotherapy
2-09-87	22	—	First course of cisplatin and etoposide chemotherapy
3-16-87	20	—	Second course of same treatment
4-13-87	28	<5.0	Right upper lobe lesion revealed in lung by X-ray, wedge resection of lung performed
5-07-87	36	<5.0	
5-12-87	7.7	<5.0	First course of EMA-CO
5-20-87	15	<5.0	
6-12-87	<5.0	<5.0	Second course of EMA-CO
6-30-87	<5.0	<5.0	Third course of EMA-CO
7-25-87	<5.0	<5.0	Fourth course of EMA-CO
8-3-87 to 1-17-89	<5.0	<5.0	27 $\beta$ -hCG and hCG studies with identical results

\* Intact hCG procedure introduced in our lab. as a routine serum pregnancy test.

examinations were unremarkable. Roentgenographic studies revealed a lesion in the left lung, and a computerized tomographic scan demonstrated small lesions in the frontal and left parietal lobes of the brain. Biopsies of the lungs and brain confirmed the presence of choriocarcinoma. Treatment with 4000 rads of whole-brain radiation and modified Bagshawe chemotherapy led to a reduction in  $\beta$ -hCG values (see Table 1). However, three months later, a modest increase in  $\beta$ -hCG signaled possible recurrence of a tumor. Additional chemotherapy and a hysterectomy did not suppress the  $\beta$ -hCG.

After five more months, a metastasis in the right lung,

discovered by roentgenogram, was surgically removed. This operation, along with a different chemotherapy regimen, decreased  $\beta$ -hCG to  $<5.0$  int. units/L. The patient has been in remission since August 1987.

This last metastasis was associated with an increase in  $\beta$ -hCG long before the metastasis could be demonstrated by visualization techniques. However, this increase in  $\beta$ -hCG was not paralleled by an increase in intact hCG, which remained normal ( $<5$  int. units/L), even in the presence of a documented metastasis (Table 1).

For the detection and monitoring of trophoblastic disease, this case clearly demonstrates the need for using a method that measures free  $\beta$ -hCG subunits. It also emphasizes the need to select assays that allow accurate measurement of  $\beta$ -hCG values that only slightly exceed the normal reference interval.

#### References

1. Fan C, Goto S, Furuhashi Y, Tomoda Y. Radioimmunoassay of the serum free  $\beta$ -subunit of human chorionic gonadotropin in trophoblastic disease. *J Clin Endocrinol Metab* 1987;64:313-8.
2. Hay DL. Histological origins of discordant chorionic gonadotropin secretion in malignancy. *J Clin Endocrinol Metab* 1988;66:557-64.
3. Rosen SW, Weintraub BD, Vaitukaitis JL, Sussman HH, Husiman JM, Muggia FM. Placental proteins and their subunits as tumor markers. *Ann Intern Med* 1975;82:71-83.
4. Weintraub BD, Rosen SW. Ectopic production of the isolated beta subunit of human chorionic gonadotropin. *J Clin Invest* 1973;52:3135-42.
5. Rosen SW, Weintraub BD. Ectopic production of the isolated alpha subunit of the glycoprotein hormones. *N Engl J Med* 1974;290:1441-7.
6. Gallion HH, van Nagell JR, Donaldson ES, Higgins RV. Successful salvage therapy of resistant gestational trophoblastic disease with etoposide, methotrexate, dactinomycin, vincristine, and cyclophosphamide. *Gynecol Oncol*, in press.