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Human Chorionic Gonadotropin as a Biomarker not only Pregnant Women, but also as a Marker in Men – Testicular Cancer – Review and Case Report

Vinceova A[1]* and Bartko Ch[2]

[1]Gynecology-obstetrics clinics, Comenius University, Bratislava, Slovakia

[2]Surgical clinisc, Comenius University, Bratislava, Slovakia

***Corresponding author:**

Vinceova A,
Gynecology-obstetrics clinics, Comenius University, Bratislava, Slovakia

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1. Summary

Human chorionic gonadotropin is a hormone produced primarily by syncytiotrophoblastic cells of the placenta during pregnancy. The hormone stimulates the corpus luteum to produce progesterone to maintain the pregnancy. Smaller amounts of hCG are also produced in the pituitary gland, the liver, and the colon. Human chorionic gonadotropin (hCG) levels correlate with clinical disease burden. Exceptionally high levels of hCG were detected in a small subgroup of patients with seminoma. Four percent of patients with advanced disease had hCG levels ≥2000 IU/l associated with a poor prognosis [1].

2. Introduction

Human chorionic gonadotropin (hCG) is a chemical created by trophoblast tissue, tissue typically found in early embryos and which will eventually be part of the placenta. Measuring hCG levels can be helpful in identifying a normal pregnancy, pathologic pregnancy, and can also be useful following an aborted pregnancy. There is also a benefit in measuring hCG in a variety of cancers including choriocarcinoma and extra-uterine malignancies.

3. Etiology and Epidemiology

Human chorionic gonadotropin is a hormone produced primarily by syncytiotrophoblastic cells of the placenta during pregnancy. The hormone stimulates the corpus luteum to produce progesterone to maintain the pregnancy. Smaller amounts of hCG are also produced in the pituitary gland, the liver, and the colon. As previously mentioned, certain malignancies can also produce either hCG or hCG-related hormone. Trophoblastic cancers (hydatidiform mole, choriocarcinoma, and germ cell tumors) are associated with high serum levels of hCG-related molecules.

The hormone itself is a glycoprotein composed of two subunits, the alpha and beta subunits. There are multiple forms found in the serum and urine during pregnancy including the intact hormone and each of the free subunits. HCG is primarily catabolized by the liver, although about 20% is excreted in the urine. The beta subunit is degraded in the kidney to make a core fragment which is measured by urine hCG tests [2].

4. Testing

1) Urine - after drinking small amount of fluid, best in the morning the first urine, to get precise results, and not to get falsely negative test. Blood in the urine can also cause false results

2) Serum - taking peripheral blood for a serum hCG testing (Table 1 and 2).

The median free β-hCG concentration in Down's syndrome pregnancies was 2.22 MoM (95% confidence interval (CI), 1.84–2.68 MoM), significantly higher than that in unaffected pregnancies ($P<0.001$). An elevated β-hCG in the absence of viable pregnancy can occur for multiple reasons and has a broad differential diagnosis including miscarriage, ectopic pregnancy, pituitary hCG production, trophoblastic disease and phantom hCG. hCG levels may be higher than normal for many different reasons. The level of hCG in your blood may be higher than normal because you are pregnant or you have a certain kind of bowel disease, a stomach

ulcer or cirrhosis of the liver. Your hCG level can also be high if you smoke cannabis (marijuana).

In summary hCG levels don't correspond the physiological levels in cases of:

- Down's syndrome
- Miscarriage
- Ectopic pregnancy
- Hydatidiform mole
- Trophoblastic disease
- Phantom hCG
- Breast cancer
- Multiple myeloma
- Gastric cancer
- Hepatocellular carcinoma
- Testicular cancer
- Pancreatic cancer

This raises the cautiousness for clinicians especially finding either pathological levels of hCG or finding any levels of hCG in men.

Table 1: hCG levels during pregnancy

Weeks of pregnancy	*Levels of hCG*
3	5-50 mIU/ml
4	5-426 mIU/ml
5	18-7340 mIU/ml
6	1080-56500 mIU/ml
07-Aug	7650-229000 mIU/ml
09-Dec	25700-288000 mIU/ml
13-16	13300-254000 mIU/ml
17-24	4060-165400 mIU/ml
25-40	3640-117000 mIU/ml
Non pregnant	55-200 mIU/ml

Table 2: hCG levels in serum according to different age and status

Category	*hCG levels (IU/L)*
Premenopausal (18-40 years), non pregnant	<5
Perimenopausal (41-55 years),non pregnant	<8
Postmenopausal (55 years and higher)	<14
Early normal pregnancy	>5 0
Pregnancy, second-third trimester	273000-233000
Gestational trophoblastic neoplasia	>100000

5. Testicular Cancer

Testicular cancer happens when cells in the testicle grow to form a tumor. This is rare. More than 90 percent of testicular cancers begin in the germ cells, which produce sperm. There are two types of germ cell cancers (GCTs). Seminoma can grow slowly and respond very well to radiation and chemotherapy. Non-seminoma can grow more quickly and can be less responsive to those treatments. There are a few types of non-seminomas: choriocarcinoma, embryonal carcinoma, teratoma and yolk sac tumors.

In 2023, an estimated 9,190 people in the United States will be diagnosed with testicular cancer. About 1 out of every 250 men and boys will be diagnosed with the disease during their lifetime. Worldwide, an estimated 74,458 people were diagnosed with testicular cancer in 2020.

Testicular cancer can occur at any age, but is most often found among males age 20 to 44 years. The most common tumor type among males younger than 30 years was non-seminoma germinoma. The most common tumor type among older males was seminoma germinoma (3). The average age of males when first diagnosed with testicular cancer is about 33. This is largely a disease of young and middle-aged men, but about 6% of cases occur in children and teens, and about 8% occur in men older than 55 [4].

6. Diagnosis by Serum Tumor Markers

Mostly patients come to the doctor with the finding of inguinal and pelvic lymphadenopathy. The lump in the testicle can occur in some cases, mostly the tumor itself is just few milimeters.

Tumor markers (AFP, HCG, and LDH) should be measured before any treatment, such as surgery. If cancer is found, tumor marker tests will be repeated after treatment to track how well you're doing over time. Some medicines and marijuana can create false positive levels of HCG. Tell your doctor about your medicine and/or marijuana use. It is also worth noting that:

* Pure seminomas can raise HCG levels but never AFP levels
* Non-seminomas often raise AFP and/or HCG levels
* Over the counter urinary pregnancy tests do check for HCG levels in the urine but are not reliable tests for testicular cancer [5].

7. TNM Classification of Testicular Cancer

7.1. T: tumor

Primary tumor staging is from histological assessment following orchiectomy:

Tx: primary tumor cannot be assessed (orchiectomy not performed)

T0: no evidence of primary tumor

Tis: intratubular germ cell neoplasia (carcinoma in situ)

T1:

tumor limited to testis and epididymis

may invade tunica albuginea

may not invade tunica vaginalis

no vascular or lymphatic invasion

T2:

tumor limited to testis and epididymis

involvement of tunica vaginalis

vascular or lymphatic invasion

T3: invasion of spermatic cord

T4: invasion of scrotum

7.2. N: nodes

Abdominal retroperitoneal nodes are considered regional lymph nodes. A CT short axis measurement threshold of 7-8 mm has 70% sensitivity and specificity for malignant involvement or retroperitoneal nodes 4. The largest dimension of a lymph node is used to differentiate between N1-N3.

Nx: nodes cannot be assessed

N0: no evidence of nodal involvement

N1: one or more lymph nodes involved but all <2 cm in greatest dimension

N2: one or more lymph nodes involved 2-5 cm in greatest dimension

N3: one or more lymph nodes involved >5 cm in greatest dimension

7.3. M: metastases

Mx: presence of metastases cannot be assessed

M0: no evidence of metastases

M1: distant metastases present

M1a: non-regional lymph node or pulmonary metastases

M1b: distant metastases not fulfilling M1a [6].

8. Testicular Cancer Treatment

Surgery is the most common treatment for testicular cancer. Usually it mean radical inguinal orchiectomy. There is also a possibility to perform retroperitoneal lymphonodectomy in case of affected lymph nodes or suspicion of metastasion of cancer. Malignant testicular cancers metastasize in a predictable fashion through the lymphatic system unless the lymphatic drainage from the testes has been altered from prior procedures [7]. Testicular cancer spreads mostly to the lung and the lymph nodes of the chest, pelvis, or neck. More advanced stages metastase into the liver and bones. Testicular cancer rarely spreads to the brain unless the primary tumor is a choriocarcinoma.

Chemotherapy is both a primary treatment option but may typically be reserved for relapses in these patients. The recommended treatment for selected stage IIB, all IIC and all stage III seminoma patients is chemotherapy [8].

9. Case Report

26-year-old patient with finding of inguinal and pelvic lymphadenopathy. In examination of ultrasound and CT imaging there were findings of typical oval enlargement of lymph nodes. After serologic examinations which excluded other diseases that cause the lympadenopathy, there has been taken tumor marker HCG, which diagnosed and verified the diagnosis of testicular carcinoma – seminoma. By CT examination there were findings of three lesions in liver. Planning therapy was set for orchiectomy followed by chemotherapy and radiotherapy. From diagnostic and prognostic reasons, according to the fact that the lymphadenopathy will be cured, but lesions in liver will stay without pathologic absorption of contrast but will remain uncured, therefore for indication of oncologist, the patient underwent non-anatomical wedge resection of the three lesions for histopathologic examination (Figure 1). Histopathologic showed fibrotic changes of the tissue after chemotherapy. There were none perioperative or postoperative complications and patient lives up to date without any signs of recurrence.

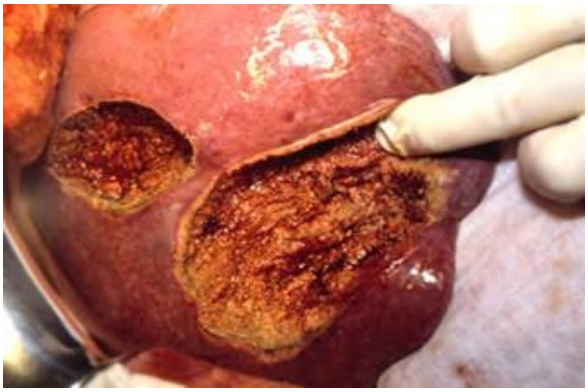

Figure 1: Wedge resection of the liver lesions sent to histopathological examination after chemotherapy

10. Discussion

In cases of inguinal and/or pelvic lymphadenopathy in men in typical age of late 20s and early 30s, in non-palpable tumor or growth of testis, the examination of HCG tumor marker and itś positive testing, very easy method of fast diagnosis of testicular carcinoma.

With advancements in knowledge about the epidemiology, pathophysiology, and evaluation modalities, advanced management options are now available. With cure rates as high as 90% and >95% 5-year survival rate, testicular cancer is one of the most curable malignancies [9].

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