CLINICAL VIGNETTE

Elevated β-hCG in a Non-Pregnant Patient

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Case

A 45-year-old woman was admitted to neurology for an evaluation of paresthesias and intermittent bowel and urinary incontinence that began several weeks prior. She lives in Nevada and was advised to seek evaluation at the University after extensive previous workup was unrevealing. The patient present to the Emergency Department with results from prior serologic studies for autoimmune and paraneoplastic causes as well as prior lumbar puncture bone marrow biopsy and electromyogram, which were also negative. Initial UCLA labs were significant for neutropenia of 3 x 10 (4.16-9.95 x 10E3/microL), low serum copper of <10 ug/dL (80.0-155.0 ug/dL), and positive serum and urine pregnancy tests. Imaging included chest X-ray, MRI C/T/L spine with and without contrast, and MRI of the brain without contrast, which were unremarkable. Neurology felt many of the patient's symptoms were related to copper deficiency from prior obesity surgery, but consulted Internal Medicine for the positive pregnancy test in a patient who was not sexually active.

Past medical history included neutropenia for one year. Prior surgery included Total abdominal hysterectomy with L Salpingo-oophorectomy and gastric bypass 15 years prior. Repeat serum pregnancy test, was also positive. Quantitative total beta human chorionic gonadotropin (hCG) test was slightly elevated at 10 mIU/mL (Ref: <=5 mIU/mL in non-pregnant females). Repeat total beta hCG testing confirmed the mild elevation at 9 mIU/mL.

Assessing the Cause of Elevated hCG

The differential diagnosis of elevated hCG includes malignant and non-malignant sources. Nonmalignant etiologies include: pituitary hCG, exogenous hCG, heterophilic antibodies, and familial hCG syndromes. Malignant etiologies such as active gestational trophoblastic disease (GTD), quiescent gestational trophoblastic disease (Q-GTD), and ectopic production from non-trophoblast malignancies such as ovarian, cervical, and lung malignancies.[1,2]

In this patient, pituitary hCG was considered the most likely etiology given her age and her degree of beta hCG elevation which was within the typical range (< 25 mIU/ml)[3] seen in pituitary hCG in peri- or postmenopausal patients. Other non-malignant causes of elevated hCG were considered unlikely. The presence of heterophilic antibodies ("phantom hCG") was ruled out due to her positive urine pregnancy test, as heterophilic antibodies are not excreted in urine. Exogenous hCG is most often associated with fertility treatment and was ruled out based on history. Familial hCG syndrome is an exceedingly rare condition that is considered only after more common etiologies have been assessed,[4] and was thought to be unlikely in this patient.

While pituitary hCG was the most likely source, malignant etiologies were also considered. The team was concerned about a possible malignancy given the patient's previous hysterectomy. She reported the hysterectomy was performed for an adnexal cyst and denied any personal or family history of gynecologic cancer or abnormal uterine bleeding. Gestational trophoblastic disease (GTD) was unlikely in this patient given her history of hysterectomy and because hCG levels in GTD are typically in the range of 50,000 to 100,000 mIU/ml.[5] Quiescent gestational trophoblastic disease (Q-GTD) is associated with lower levels of hCG elevation than active GTD, but levels are still typically 50-100 mIU/ml.[5] The level of hCG elevation associated with non-trophoblastic malignancies is less clearly defined, and requires evaluation with additional laboratory testing and imaging for conclusive evaluation. To further evaluate for gynecological malignancies, basic tumor markers were obtained and returned normal. CA-125 was 10 (normal range: 0-35 U/mL) and AFP was <1.82 (normal range of 0-6.7ng/mL).

The presence of pituitary hCG was assessed with an endocrine evaluation including normal thyroid function tests, FSH of 109 mIU/mL (post-menopausal: 21-106 mIU/mL), and LH of 76.9 mIU/mL (post-menopausal: 16-63 mIU/mL) consistent with menopause. The patient was diagnosed with perimenopausal pituitary hCG given her elevated LH and FSH levels and the absence of other significant findings. However, she was also scheduled for outpatient oncology follow-up and transvaginal ultrasound.

Understanding Pituitary hCG

During pregnancy, hCG is primarily produced by syncytiotrophoblastic cells of the placenta. hCG plays an important role during pregnancy, as it stimulates the production of progesterone by the corpus luteum, helping to maintain the endometrial lining and prevent menstruation.[6] Outside of pregnancy, low levels of hCG can also be produced by the anterior pituitary gland under the control of gonadotropins.

Patients with primary hypogonadism, have low levels of sex hormones, which lead to a reduction in the estrogen-associated negative feedback of gonadotropin-releasing hormone (GnRH), which, in turn, leads to increased production of luteinizing hormone (LH) and follicle stimulating hormone (FSH). It is thought that increased gene expression of LH could be responsible for elevated pituitary hCG due to the LH beta-subunit gene located between multiple hCG beta-subunit genes. The proximity of these genes could explain why elevated expression of LH leads to elevated expression of pituitary hCG. Additionally, the beta-subunit of hCG is 80-85% homologous to LH.[7] As a result, some receptors for LH can also recognize hCG and vice versa. The structural similarities between these two molecules may also play a role in elevated pituitary hCG.

High levels of pituitary hCG in patients with gonadal failure, such as after menopause, or bilateral oophorectomy, can lead to false positive pregnancy tests. False positive hCG pregnancy tests are found in approximate 1% of perimenopausal patients and 7% of postmenopausal patients.[8] Assessing patients for pituitary hCG can be done by measuring gonadotropins, such as FSH. An FSH level of >30mlU/mL is consistent with pituitary Hcg.[7] The diagnosis of pituitary hCG can also be confirmed by providing exogenous estrogen in the form of combined estrogen-progestin oral contraceptives for 2-3 weeks.[9] Increased estrogen will lead to negative feedback on GnRH and subsequently cause pituitary hCG levels to fall. Once a diagnosis is confirmed, no treatment is necessary for pituitary hCG.

Conclusion

Pregnancy tests are routinely performed on patients upon arrival at the hospital and prior to imaging studies or procedures that could be harmful to a fetus. hCG levels can be elevated in the absence of pregnancy or malignancy in pituitary hCG associated with peri- or postmenopausal states. A false positive pregnancy test and incidental finding of elevated hCG in a non-pregnant patient presents a diagnostic dilemma, as providers often feel the need to perform additional testing to rule out malignant causes. Studies have shown that incidental findings of elevated pituitary hCG in peri- and postmenopausal patients can lead to delays in diagnostic evaluations and treatments for other medical problems, as well medically inappropriate treatments, such as chemotherapy or surgery to address the elevated hCG.[9]

To prevent patients from undergoing unnecessary testing and interventions for pituitary hCG, clinicians should consider the risks and benefits of evaluating a patient with elevated hCG in the absence of pregnancy. A proposed approach from Hage et al suggests that further evaluation of elevated hCG is not recommended in peri- or postmenopausal patients unless the hCG levels are greater than 14 IU/L and FSH levels are 40 IU/L or less. In patients with hCG levels higher than 14 IU/L and FSH levels lower than 40 IU/L, providers should employ the USA hCG Reference Service protocol to direct medical decision-making.[9] Confirming the presence of a malignancy with biochemical testing should always be done before initiating therapy or recommending surgery to treat patients with elevated hCG. When a diagnosis of pituitary hCG is made following a false positive pregnancy test, providers should provide counseling about the patients' risk for future false positive pregnancy tests and recommend patients inform clinicians of this diagnosis to prevent unnecessary repeat evaluations.[10]

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