Persistently Elevated Human Chorionic Gonadotropin in a Menopausal Woman

Article:
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Guest:
Dr. Anna Merrill is a Clinical Chemistry Fellow at the University of Washington in Seattle. .

Randye Kaye: Hello, and welcome to this edition of "JALM Talk" from *The Journal of Applied Laboratory Medicine*, a publication of the American Association for Clinical Chemistry. I'm your host, Randye Kaye.

Human Chorionic Gonadotropin or hCG is a glycoprotein secreted by the placenta that plays a key role in maintaining pregnancy, during which serum concentrations become elevated. However, aberrant hCG secretion can also occur in cancer, particularly in germ cell tumors and in gestational trophoblastic disease. The current FDA-approved immunoassays for HCG are only approved for use and detection of pregnancy and not as a tumor marker, and are prone to analytical false positives and false negatives. However, false positives may also be physiological.

A Case Report entitled "Persistently Elevated hCG in a Menopausal Woman," published in the November 2016 issue of JALM, discussed a patient on whom a serum hCG test was performed due to suspicion of ovarian cancer. The case discussion highlights the nuances of hCG assay interpretation in terms of analytical interferences and potential physiological causes of elevated hCG concentrations, as well as recommendations for laboratories and physicians in interpreting assay results.

The first author of this article is Dr. Anna Merrill, a Clinical Chemistry Fellow at the University of Washington in Seattle. Dr. Merrill is our guest for today's podcast. Welcome, Dr. Merrill. Why should hCG even be ordered in a patient like the one in this Case Report?

Dr. Anna Merrill: Well, as you mentioned, Human Chorionic Gonadotropin, or hCG, is a glycoprotein that is secreted by the trophoblastic cells of the placenta. It helps to maintain the corpus luteum and stimulate synthesis of progesterone. Because of its specificity to the placenta, hCG is most commonly measured to confirm pregnancy and to monitor its progression. Our 50-year-old female patient is sexually active but her last

menstrual period occurred over two years ago and she is assumed menopausal.

So, in menopausal patients like this one, a serum hCG level was requested, not as an indicator of pregnancy, but as a tumor marker because of concerns about ovarian cancer, based on the patient's family history and on the patient's presentation with abdominal symptoms. In a menopausal patient like this one, a serum hCG level was requested not as an indicator of pregnancy, but as a tumor marker because of concerns the patient had about ovarian cancer based on her family history and on non-specific symptoms.

Interestingly, hCG has limited utility as a screening tool in this context and if used as such, may have caused this patient unnecessary worry.

Randye Kaye: Interesting but wait, I thought that hCG could be produced by some tumors? So when, if ever, is it indicated to order hCG for non-pregnancy screening?

Dr. Anna Merrill: Yes, you're right, hCG can be expressed aberrantly in certain types of gestational trophoblastic disease. The most common form is molar pregnancy and this is usually benign but it can develop into cancerous forms of gestational trophoblastic disease such as choriocarcinoma.

Elevated hCG can also be found in ovarian and testicular germ cell tumors, and rarely in other types of malignancy. But as you mentioned earlier, there is currently no commercial hCG assay that is approved by the FDA for use as a tumor marker. Now, with that said, hCG is measured in non-pregnant women to confirm removal of all residual field tissue after an abnormal pregnancy, or after early termination of pregnancy.

This is especially important when the patient is left at risk for gestational trophoblastic disease. Typically, hCG levels are measured in serum every week until they reach undetectable levels, and then hCG is continued to be monitored on a monthly basis until levels are undetectable.

Randye Kaye: I see. So, are there any other tumor markers that should be measured in those patients presenting with non-specific abdominal pain?

Dr. Anna Merrill: You know, unfortunately, there really aren't great tumor markers that are recommended for screening in the context of non-specific symptoms, such as cramping, bloating or even some spotting. Alpha-fetoprotein and hCG may be elevated in ovarian germ cell tumors, as you mentioned before, and hCG in gestational trophoblastic disease.

There is a different marker called Cancer Antigen 125, CA125, that may be recommended for ovarian cancer screening, but really only in high risk patients and even then, it's not always indicated. It is very important that clinicians demonstrate a malignancy clinically and not just based on readily available biochemical tests.

Randye Kaye: OK, so how did you know that the hCG in this patient was from the pituitary and highly unlikely to be a placental origin?

Dr. Anna Merrill: We first evaluated whether or not the elevated hCG was a false positive result analytically. So most often, these erroneous elevations are caused by antibodies within the patient's sample that end up bridging the capture and detection antibodies in the assay to produce a signal even when little or no hCG is present in the serum of the patient.

This possibility was first investigated by measuring hCG immunoreactivity on multiple assays from different manufacturers. It is important to perform this analysis on platforms from different manufacturers to ensure that different antibodies with different epitopes are used in the workup.

We next evaluated the likelihood of a false positive hCG result using serial dilutions and by treating the patient sample with a heterophile blocking tube. None of these mechanisms were able to eliminate the hCG that we were detecting in this patient. We next measured hCG in a paired urine sample using a point of care device.

Typically, if hCG can be detected in the urine, that is another sign that the hCG is physiologically real, but not too surprisingly, urine hCG in this patient was negative. However, it is well-known that many point of care tests are less sensitive than quantitative serum hCG methodologies, and therefore are prone to false negative results at low hCG concentrations like the one we were seeing in our case patient.

In addition to analytical false positive hCG results, physiological false positive hCG is also possible. In peri- and postmenopausal women for example, increased hCG has been demonstrated even though these women have no detectable placental source of hCG. The theory for these patients is that their declining ovarian function may lead to pituitary hyperstimulation. This then causes elevated concentrations of follicle stimulating hormone, or FSH, and hCG to be released from the gonadotropic cells of the pituitary. Looking for elevated FSH can pretty much, but not entirely, rule out hCG of placental origin as was the case with this patient who had elevated FSH.

This case is a helpful reminder that even commonly-ordered tests like hCG may not always be used properly. In many cases, clinicians may assume that an elevated hCG implies pregnancy or malignancy even if there is no clinical evidence that supports that diagnosis.

There will always be countless opportunities for laboratorians to collaborate with clinical colleagues on what tests to order and how the results should be interpreted.

Randye Kaye: OK, thank you. That was very interesting. Dr. Merrill, thank you so much for joining us today.

Dr. Anna Merrill: Thank you for the invitation to participate.

Randye Kaye: That was Dr. Anna Merrill from the University of Washington in Seattle, talking about the JALM Case Report, “Persistently Elevated hCG in a Menopausal Woman.” Thanks for tuning in for “JALM Talk.” See you next time and don’t forget to submit something for us to talk about.