Clinical Chemistry Trainee Council
Pearls of Laboratory Medicine
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TITLE: Tumor Markers: Alpha-fetoprotein (AFP) and human Chorionic Gonadotropin (hCG)

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Slide 1: Introduction

Hello, my name is Dr. Yan Zhang. I am an Assistant Professor in the Department of Pathology and Laboratory Medicine at the University of Rochester Medical Center and Associate Director of Clinical Chemistry and Toxicology Laboratories at Strong Memorial Hospital. Welcome to this Pearl of Laboratory Medicine on "Tumor Markers: Alpha-fetoprotein (AFP) and human Chorionic Gonadotropin (hCG)."

Slide 2: Alpha-fetoprotein (AFP)

Alpha-fetoprotein or AFP is the major protein in fetal circulation and is closely related to albumin both genetically and structurally. It is one of the oncofetal antigens produced during fetal life and has a high concentration in the sera of fetuses. This concentration decreases to low levels or becomes undetectable after birth, although it may increase in some malignancies, such as hepatocellular carcinoma.

AFP is a single-chain glycoprotein with a molecular weight of around 70 KDa and 4% carbohydrate content. However, tumor cell-derived AFP has various carbohydrate compositions depending on the saccharide transferase activity within the tumor cells.

Slide 3: Human Chorionic Gonadotropin (hCG)

Human chorionic gonadotropin (hCG) is also a glycoprotein secreted by the syncytiotrophoblastic cells of the normal placenta. Its concentration is highly elevated during pregnancy. For details of its specific function during pregnancy, please refer to the Pearl of Laboratory Medicine on hCG by Dr. David Grenache. This session will focus on hCG's functions as a tumor marker.

Slide 4: AFP and hCG as Tumor Markers

This slide summarizes how AFP and hCG function as tumor markers. AFP and hCG have been commonly used as markers for hepatocellular carcinoma and trophoblastic disease, respectively. In addition, AFP and hCG are used together as markers for germ cell carcinoma. In the next few slides, we will review their functions in these different types of tumors.

Slide 5: AFP in Hepatocellular Carcinoma

AFP is often increased in cancer, especially when the level of AFP > 1000 µg/L, at which about 50% of hepatocellular carcinoma (HCC) can be detected. Another 50% of HCC has normal to lower AFP concentrations. In general, AFP > 500 µg/L is a threshold that would suggest the need for a biopsy. The serum concentration of AFP is loosely related to the size of HCC tumors. In order to detect early stage or small tumors less than 5cm in size, the AFP cutoff is typically set at a concentration of 10 – 20 µg/L.

There have been no randomized clinical trials showing a mortality risk benefit from the use of AFP as a screening tool for HCC. However, retrospective studies performed in Asia have suggested improved survival with AFP screening. It is not recommended for clinical screening purposes. AFP has been used as a diagnostic tool for high risk areas such as China, Africa, Japan, and Alaska where the prevalence of hepatocellular carcinoma is high.

Slide 6: AFP in Hepatocellular Carcinoma

AFP can also be used for the prognosis and monitoring of treatment of HCC. An increased AFP level of > 10 µg/L and an elevated serum bilirubin level of > 2mg/dL have both been shown to be associated with shorter survival times.

AFP concentration is expected to decrease after surgery to remove a tumor. Persistently high AFP after surgery may indicate incomplete removal of the tumor or the presence of metastasis. A significant increase in AFP in post-surgery tumor-free patients may also indicate metastasis. Due to the low sensitivity of AFP and the large percentage of HCC patients who don't have highly elevated AFP, the follow-up AFP concentration changes are best used to detect recurrence in those who have elevated AFP before treatment.

Slide 7: Specificity of AFP for HCC

The specificity of AFP for HCC is low, which limits AFP's use for general screening purposes. Elevated AFP can also be seen in benign liver conditions, such as hepatitis and cirrhosis, as well as other types of cancers such as stomach, colon, lung, breast cancer, and lymphoma. However, the concentrations of AFP in these conditions are typically < 200 µg/L.

Slide 8: hCG in Trophoblastic Tumors

A trophoblastic tumor is a proliferation of cells derived from the placenta. Trophoblastic tumors can produce very elevated concentrations of hCG in the serum that may exceed 1 million IU/L. The serum concentration of hCG is correlated with the size of the tumor, although hCG is not particularly specific to trophoblastic tumors. Elevated hCG can also be seen in 70% of nonseminomatous testicular germ cell tumor patients, 45 – 60% of biliary and pancreatic cancer, and 10 - 30% of bladder, renal, prostate, liver, colorectal, lung, breast, head, and neck cancers. Therefore, hCG is not recommended for general screening of trophoblastic tumors.

Slide 9: hCG in Trophoblastic Tumors

hCG is also useful to indicate the prognosis of trophoblastic tumors. Its serum concentration is correlated with tumor size and tumor prognosis. In particular, the concentration of the hyperglycosylated form may help in tumor prognosis. The hyperglycosylated form can also aid in the early detection of new or recurrent trophoblastic malignancy as well as discriminate active from quiescent trophoblastic neoplasia.

Please note that hCG is unable to pass the blood-brain barrier. An elevated level of hCG in the cerebrospinal fluid may indicate metastasis to the brain.

Slide 10: hCG in Trophoblastic Tumors

The most useful function of hCG in trophoblastic tumors is in monitoring the treatment and progression of the disease. During chemotherapy, it is recommended that hCG be monitored on a weekly basis. After remission, hCG should be monitored on a yearly basis to detect possible relapse.

The concentration of hCG correlates with tumor volume and progression. An initial hCG concentration of more than 400,000 IU/L may indicate a high risk of treatment failure. In addition, a slow decrease in hCG post-surgery may indicate residual disease.

Slide 11: hCG Analytical Concerns

Since tumor cells may only secrete free beta subunits of hCG, it's important to measure total beta-hCG when there is a suspicion that a tumor is present. It's also important for the assay to have equal molar recognition of intact hCG and hCG beta subunits, so that the concentrations of the intact or the beta subunits will not be underestimated in the samples. The hCG assays should have less than 2% cross-reactivity with luteinizing hormone. Although it's a challenge for most of the commercial assays, it's desirable for hCG assays to reach less than 1 IU/L limit of detection for tumor detection, as recommended by the National Academy of Clinical Biochemistry.

Slide 12: AFP and hCG for Testicular Tumors

AFP and hCG have been used as classification and staging markers for germ cell tumors. In this session, testicular tumors will be used as an example to illustrate these functions, as about 95% of testicular cancers are of germ cell origin. To summarize, AFP and hCG can be used for the diagnosis, staging, risk stratification, and monitoring response to therapy for testicular cancer patients.

It's mandatory to measure AFP and hCG before treatment if testicular cancer is suspected. In seminoma patients, hCG is usually < 300 IU/L, while it is > 1000 IU/L in nonseminomatous germ cell tumors. Note that if AFP is also elevated, the tumors are reclassified as nonseminomatous germ cell tumors.

With respect to their functions in the prognosis of testicular cancer, an hCG of < 5000 IU/L and an AFP of < 1000 µg/L suggest a good prognosis. However, highly elevated hCG and AFP levels when hCG > 50,000 IU/L and AFP > 10,000 µg/L suggest a poor prognosis. Any numbers in between indicate intermediate prognosis.

Slide 13: AFP and hCG for Testicular Tumors

If AFP and/or hCG are at increased levels before therapy, the rate of decline in tumor marker concentration reflects the patient's response to therapy. Monitoring AFP and/or hCG weekly post-therapy until the levels fall into the reference intervals is therefore recommended. Persistent elevations of tumor markers after chemotherapy indicate residual disease and the potential need for further therapy. Half-lives should also be determined whenever possible during the course of therapy. When there is no residual disease, the half-lives of hCG and AFP are 1.5 days and 5 days respectively. During chemotherapy, prolonged half-lives of hCG and AFP such as 3.5 days and 7 days, respectively, may indicate recurrence and an adverse prognosis.

After successful initial therapy, serial monitoring is recommended for surveillance. Relapse is most likely to occur within the first year and is very rare after two years. However, relapse in patients 10 years post-therapy has been observed. The frequency of surveillance is determined by the type of tumor, growth stage, treatment, and the likelihood of relapse. For instance, patients with nonseminomatous germ cell tumors after inguinal orchiectomy should be monitored every one to two months for the first two years. The frequency should be gradually decreased to every six months in year three and then annually beginning in year five.

One message to bear in mind is that lactate dehydrogenase has also been used as a tumor marker for testicular cancer with similar functions to AFP and hCG in disease diagnosis, prognosis, monitoring of therapy, and surveillance.

Slide 14: References

Slide 15: Disclosures

Slide 16: Thank You from www.TraineeCouncil.org

Thank you for joining me on this Pearl of Laboratory Medicine: "Tumor Markers: Alpha-fetoprotein (AFP) and human Chorionic Gonadotropin (hCG)." I am Yan Zhang.