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Tumor Markers- A Review

Dr. Kandukuri Mahesh Kumar*
Assistant Professor, Nizam's Institute Of Medical Sciences, Hyderabad, Telangana State, India

Review Article

***Corresponding author**
Dr. Kandukuri Mahesh Kumar

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Abstract: They include Cell surface antigens; Cytoplasmic proteins, Enzymes, Hormones and most of them are proteins. They can be products of cancer cells themselves or of the body in response to cancer or other conditions. A marker represents a qualitative or quantitative alteration or deviation from normal of a molecule, substance, or process that can be detected by some type of assay. An elevated level of a tumor marker can indicate cancer; however there can also be other causes of the elevation. Thus, Tumour markers cannot be construed as primary modalities for the diagnosis of cancer. These tumor markers help in screening, diagnosing the diseased condition, staging of the disease, guiding and monitoring the treatment, to determine the prognosis and to prevent recurrence.

Keywords: Tumor Markers, Cancer, CarcinoEmbryonic Antigen, Alpha Fetoprotein, Cancer Antigen, Malignancy.

INTRODUCTION

A tumor marker is biomarker found in blood, urine, or body tissues that can be elevated by the presence of one or more types of cancer. There are different tumor markers few are organ specific and few are specific for the tumor type, each indicative of a particular disease process, and they are used in oncology to help detect the presence of cancer. An elevated level of a tumor marker can indicate cancer of that particular tissue or organ; however, there can also be other causes of the elevation which needs to be ruled out with other investigations.

Tumor markers can be produced directly by the tumor or by non-tumor cells as a response to the presence of a tumor. There are few diagnostic modalities for tumor markers like Mammography, Ultrasonography, Computed tomography (CT) and Magnetic Resonance Imaging scans (MRI) help in the staging and treatment of the various carcinomas; they are usually not definitive diagnostic tests. The definitive diagnosis is mostly confirmed by biopsy and histopathological examination of the tissue. Based on their biochemical nature, these tumor markers can be simple proteins, conjugated proteins, peptides / polypedtides or carbohydrates. Proteins or conjugated proteins may be enzymes, hormones or fragments of proteins. The first success in developing a blood test for a common cancer was in 1965, when Carcinoembryonic antigen (CEA) was found in the blood of some patients with colon cancer. By the end of 1970s several other blood tests had been developed for different cancers.

TYPES OF TUMOR MARKERS

Tumor markers can be classified into two groups:

- Tissue specific markers
- Cancer specific markers

Tissue Specific Markers are related to specific tissues which have developed cancer. Generally, these substances are not related to the tumor, and may be present at elevated levels when no cancer is present. But, elevated levels point to a specific tissue being at fault. They include Prostate Specific Antigen (PSA), Beta- Human Chorionic Gonadotropin (beta-HCG), Alpha Fetoprotein (AFP), Alpha Fetoprotein L3 (AFP L3) , Thyroglobulin etc.

Cancer Specific Markers are related to the presence of certain cancerous tissue. Because there is a large overlap between the many different tumor tissue types and the markers produced, these cancer tissue might not be specific in making a diagnosis. They include Carcinoembryonic Antigen (CEA), CA 19-9, CA125, CA 15-3, CA 27-29, and BTA.

TISSUE SPECIFIC MARKERS

Prostate Specific Antigen

Prostate-specific antigen (PSA) is a glycoprotein produced by prostatic epithelium. The PSA level can be elevated in prostate cancer, prostatitis, benign prostatic hypertrophy (BPH), and prostatic trauma. It is a protein made by cells of the prostate gland, which is responsible for making some of the liquid in semen.

The level of PSA in the blood can be elevated in prostate cancer, but PSA levels can be affected by other factors as well. Men with benign prostatic hyperplasia (BPH), a non-cancerous growth of the prostate, have higher levels. The PSA test is very valuable in the follow up of patients with prostate cancer [1].

BETA- HCG

The beta subunit of human chorionic gonadotropin (b-hCG) normally is produced by the placenta. Elevated beta-hCG levels most commonly are associated with pregnancy, germ cell tumors, and gestational trophoblastic disease. False-positive levels occur in hypogonadal states and with marijuana use. In patients with extragonadal disease or metastasis at the time of diagnosis, highly elevated AFP or beta-HCG values can be used in place of biopsy to establish a diagnosis of non-seminomatous germ cell tumor. AFP values in excess of 10,000 ng per ml or b-hCG levels above 50,000 m IU per ml at initial diagnosis is associated with poor prognosis, with a five-year survival rate of 50 percent. Along with human placental lactogen (hPL), it is a useful marker for trophoblastic disease (partial and complete hydatidiform moles, gestational choriocarcinoma etc) [2].

Alpha- Fetoprotein

Alpha-fetoprotein (AFP) is the major protein of fetal serum but falls to an undetectable level after birth. The primary malignancies associated with AFP elevations are hepatocellular carcinoma and non-seminomatous germ cell tumors. Other gastrointestinal cancers occasionally cause elevations of AFP, but rarely to greater than 1,000 ng per ml. Patients with cirrhosis or viral hepatitis may have abnormal AFP values, although usually less than 500 ng per ml. Pregnancy also is associated with elevated AFP levels, particularly if the pregnancy is complicated by a spinal cord defect or other abnormality. Along with b-hCG, AFP (alpha fetoprotein) is used in the management of non-seminomatous germ cell tumors [3].

TSH, Calcitonin and Thyroglobulin

Serum thyroid-stimulating hormone (TSH) is a very sensitive measure for hyperthyroidism /hypothyroidism.

A sensitive TSH assay is useful in the evaluation of solitary thyroid nodules. A low serum TSH value suggests an autonomously functioning nodule, which typically is benign. However, malignant disease cannot be ruled out on the basis of low or high TSH levels. Other thyroid function tests are usually not necessary in the initial workup [4]. Serum thyroglobulin measurements are not helpful diagnostically because they are elevated in most benign thyroid conditions. Serum thyroglobulin level is a tumor marker for papillary, follicular, and Hu¨rthle cell thyroid cancers [4]. Thyroid-stimulating hormone, thyroglobulin, and antithyroglobulin antibody levels are measured postoperatively to guide decision-making regarding the use of radio-iodine, to adjust dosage of levothyroxine, and to monitor for recurrence [4]. Elevated serum calcitonin levels are highly suggestive of Medullary Thyroid Carcinoma (MTC).

CANCER SPECIFIC MARKERS

CarcinoEmbryonic Antigen

Carcinoembryonic antigen (CEA), an oncofetal glycoprotein, is expressed in normal mucosal cells and over expressed in adenocarcinoma, especially colorectal cancer. Carcinoembryonic antigen is a longstanding marker of prognosis and recurrence. However it is nonspecific and can be elevated in numerous benign or malignant conditions. Thus, an elevation in CEA is not diagnostic. Nevertheless, approximately 80% of patients with metastatic disease demonstrate CEA elevation. In the NCCN Guidelines, measurement of CEA is recommended at baseline in all patients with a diagnosis of colorectal cancer and after completion of adjuvant therapy as surveillance for recurrence [5].

Cancer Antigen 19-9

Elevated levels of CA 19-9, an intracellular adhesion molecule, occur primarily in patients with pancreatic and biliary tract cancers but also have been reported in patients with other malignancies. Elevated in 35% of patients with endometrial cancer. It is mainly used in follow-up evaluation of borderline ovarian tumors. It is not specific for ovarian cancer [6].

Cancer Antigen 125

CA 125 is a glycoprotein normally expressed in coelomic epithelium during fetal development. This epithelium lines body cavities and envelops the ovaries. Elevated CA 125 values most often are associated with epithelial ovarian cancer, although levels also can be increased in other malignancies. CA 125 levels are elevated in about 85 percent of women with ovarian cancer, but in only 50 percent of those with stage I disease. Higher levels are associated with increasing bulk of disease and are highest in tumors with non-mucinous histology. Multiple benign disorders also are associated with CA 125 elevations, presumably by stimulation of the serosal surfaces. Insensitivity in early-stage disease and low disease prevalence limit the usefulness of CA 125 in ovarian cancer screening. Elevated CA 125 levels during follow-up nearly always indicate ovarian cancer recurrence [7].

CA 27.29

Cancer antigen (CA) 27.29 is a monoclonal antibody to a glycoprotein (MUC1) that is present on the apical surface of normal epithelial cells. CA 27.29 is highly associated with breast cancer, although levels are elevated in several other malignancies. CA 27.29 also can be found in patients with benign disorders of the breast, liver, and kidney, and in patients with ovarian cysts [8].

Human Telomerase Reverse Transcriptase

Human telomerase reverse transcriptase (hTERT) is used as a biomarker in ovarian and uterine cancers. It could probably have a role in the early diagnosis of cervical cancer and cervical intra-epithelial neoplasia (CIN). Upregulation of hTERT may be a pathogenic mechanism in CIN.

Inhibin

It reaches a peak in the follicular phase of menstrual cycle and it is not detected in serum in post-menopausal women. It can be used for the diagnosis of primary and recurrent granulosa cell tumors and mucious ovarian epithelial tumors. There are two forms inhibin A and B; both are elevated in these tumors. Free alpha sub-unit of inhibin can also be measured.

Mullerian Inhibitory Substance (MIS)

Like inhibin it is undetectable in serum in post-menopausal women. It is highly specific for ovarian granulosa cell tumors.

Topoisomerase II

It is a promising marker for advanced epithelial ovarian cancers. Other recent markers in ovarian cancer include lysophosphatidic acid (a lipid found to be elevated in serum and ascites fluid), mesothelin, HE4, osteopontin, vascular endothelial growth factor (VEGF), and interleukin 8, macrophage colony stimulating factor, and different kallikreins. These markers though promising are yet to be approved in actual clinical scenario.

Estradiol

It is also used in granulosa cell tumors, but is not sensitive enough; about 30% of tumors do not produce estradiol.
It can be used to detect recurrence.

COMMON CANCERS AND ASSOCIATED TUMOR MARKERS

BLADDER CANCER

No urinary tumor markers are recommended for bladder cancer screening, although the bladder tumor antigen (BTA) and the NMP22 tests can be used along with cystoscopy (using a thin, lighted tube to look in the bladder for cancer) in diagnosing it. These tests are also being used to follow some patients after treatment, although cystoscopy and urine cytology-microscopic examination of urine for malignant cells are still recommended as the standard tests for diagnosis and follow-up. For advanced cancer, some of the markers used for other cancers such as CEA, CA 125, CA 19-9, and TPA may be elevated and can be used to follow patients during and after treatment.

BREAST CANCER

There are many accepted tumor markers used in breast cancer [9, 10]. Tumor markers used in screening, treatment, and surveillance of breast cancer are CA 15-3 [11], CA 27.29, carcinoembryonic antigen (CEA), estrogen-receptor (ER) [12, 13], progesterone receptor (PR) [12], human epidermal growth factor receptor 2 (HER2) [14], urokinase plasminogen activator (uPA) [15], plasminogen activator inhibitor 1 (PAI-1) [15], and certain multiparameter assays for gene expression (Mammoprint, Onco Type DX etc.) [16]. Certain markers like DNA ploidy by flow cytometry [17], p53 [18], cathepsin D [19], cyclin E [20], proteomics [21], detection of bone marrow micrometastases [22], and circulating tumor cells (CTCs) [23] are considered, but no evidence is available which would recommend them for routine clinical use.

COLORECTAL CANCER

The markers usually elevated in advanced colorectal cancer are CEA and CA 19-9, but neither of these is useful as a screening test for colorectal cancer. An elevated CEA before surgery may indicate a poorer prognosis. If it is high before surgery, the CEA should return to normal levels in about 4 to 6 weeks if the cancer has been entirely removed. Many doctors follow patients after surgery with CEA tests every 3 to 6 months or so to look for the return of the cancer. Patients are sometimes helped by finding a recurrence early so it can be removed by surgery. For most patients, however, the recurrence may be too widespread to be removed surgically. CEA is also used to follow patients who are being treated for advanced or recurrent disease. The CEA level is directly proportional to cancer growth and also stage of the cancer. If the CEA is not elevated in patients with advanced or recurrent cancer, sometimes the CA 19-9 will be and can be used to follow the disease.

GESTATIONAL TROPHOBLASTIC DISEASE

Trophoblastic tumors include molar pregnancies (a pregnancy that results in a tumor of the placenta) and the more aggressive choriocarcinoma. Human chorionic gonadotropin (HCG) is elevated in these tumors. HCG testing can be used to detect these cancers in women who are no longer pregnant and whose wombs do not shrink to normal size. Measurements of HCG during treatment for trophoblastic disease are very useful in determining response to therapy.

LIVER CANCER

Cancer that starts in the liver (known as Hepatocellular carcinoma) is linked with chronic infections with hepatitis B and C viruses, and with cirrhosis from various causes. This is a common type of cancer in Southeast Asia. Liver cancers can cause elevated levels of alpha fetoprotein (AFP). Higher AFP levels occur in about 2 of 3 patients with liver cancer. An elevated AFP in someone with chronic hepatitis is often used to suggest the diagnosis of this cancer. Further testing must be done along with a biopsy to prove that there is cancer. Because liver cancer is not very common in the United States, AFP testing is not

used to test the general population for this type of cancer. Screening with AFP has been successful in parts of Asia where liver cancer is common. Sometimes the cancer is found early enough so that the patient can be cured with surgery. Because of this success, some doctors in the United States may screen their patients with cirrhosis of the liver due to hepatitis B or C.

A rising AFP level would indicate cancer (on the test readout). These markers can help diagnose the disease, although a bone marrow biopsy may be needed to confirm the diagnosis. They are also helpful in tracking the course of the disease and its response to treatment. AFP can be used to help determine the most appropriate treatment for liver cancer and to follow patients after curative surgery or other treatment.

LUNG CANCER

No tumor markers have proven useful as screening tests for lung cancer. Some of the tumor markers that may be elevated in lung cancer are the carcinoembryonic antigen (CEA) in non-small cell lung cancer and the neuron-specific enolase (NSE) in small cell lung cancer. Sometimes doctors will follow these markers to evaluate treatment results. There are many other markers that can also be followed. However, because lung cancer is fairly easily seen on chest x-rays or other imaging tests, tumor markers play a less important role. There is no tumor markers commonly used to screen for this disease, although tests for immunoglobulin can be used to help detect it or make a diagnosis. Protein electrophoresis and immunofixation can find these immune system proteins in the blood or urine of most patients with myeloma.

MALIGNANT MELANOMA

No marker is of value in finding this disease early. The markers TA-90, S-100, and some other markers can be used to test tissue samples to help diagnose melanoma in suspicious areas. Blood levels of TA-90 have been used to help determine whether the melanoma has metastasized. If the blood TA-90 level is high, there is a good chance the melanoma is metastatic. TA-90 can be elevated, however, in the absence of metastatic melanoma. Because of this, it has not been used so far to plan treatment or predict prognosis. S-100 is also elevated in the blood when the disease is widespread. This marker can also be used to look for progression of the melanoma.

MULTIPLE MYELOMA

Pieces of immunoglobulins in the urine, called Bence Jones proteins, are found in some patients with multiple myeloma. Most people with myeloma also have detectable levels of immunoglobulins, called monoclonal proteins or M-proteins, in their blood. (These proteins lead to a monoclonal spike, or M spike, on the test readout.) These markers can help diagnose the disease, although a bone marrow biopsy may be needed to confirm the diagnosis. They are also helpful in tracking the course of the disease and its response to treatment. Many patients with multiple myeloma also have higher blood levels of beta-2-microglobulin, which can also provide information on prognosis and the response to treatment.

OVARIAN CANCER

Epithelial ovarian cancer (the most common form of ovarian cancer) is linked with elevated levels of CA 125. Other markers that are sometimes measured are CA 72-4 and the LASA-P. CA 125, which is elevated in 90% of women with advanced disease, is the standard marker that most doctors use. Ovarian cancer, even when advanced, is often confined to the abdomen and pelvis and hard to find through x-ray testing. Because of this, the CA 125 is often the easiest and most effective way to measure the response to treatment, or to find recurrence of a patient's cancer. CA 125 is also being used by some doctors to screen for ovarian cancer in women with a strong family history of ovarian cancers. Such women usually get regular ultrasounds for early detection along with CA 125 measurements. CA 125 is also being studied as a single screening tool in women who have no family history of ovarian cancer. At the present time, most medical groups do not recommend CA 125 testing for ovarian cancer screening because it is not clear whether it will detect the cancer early enough to increase the cure rate. Another problem with this test is that ovarian cancer is relatively rare, and the CA 125 level can be elevated in other cancers and other conditions. Therefore, an elevated CA 125 is more likely to be due to some other cause, even though extensive testing might be required to rule out ovarian cancer.

The second most common group of ovarian cancers is the germ cell tumors. Patients with these cancers often have elevated levels of HCG and/or AFP, which are useful in diagnosis and follow-up.

PANCREATIC CANCER

No markers have been found to be helpful in screening for pancreatic cancer. The CA 19-9 marker is the most useful marker for pancreatic cancer. About 85% of people with pancreatic cancer have elevated levels of this marker in their blood higher the level, the more likely the disease has metastasized. It is also useful in patient follow-up. Patients whose CA 19-9 levels drop to normal after surgery have a much better outlook than those people whose CA 19-9 remains elevated after surgery. This marker can also be used to follow the effects of treatment on more advanced disease. Some doctors also follow the level of CEA in the blood, although it may not be as helpful as the CA 19-9 level.

PROSTATE CANCER

The most commonly used marker to detect prostate cancer is the prostate-specific antigen (PSA). Prostate cancer can often be detected in its early stages

by measuring blood levels of PSA. Levels above than 4ng/ml suggest cancer may be present, while levels above 10ng/ml strongly suggest cancer. Doctors usually recommend that men with elevated levels have their prostate gland biopsies to find out if there is cancer. Prostate cancer is often a slow growing cancer that occurs in older men. For that reason, it is not clear if screening with PSA actually saves lives. Some doctors believe that screening may cause more harm than good. It may lead some men treated for cancers that would never have caused them problems, and the treatment itself can have major side effects. Large studies now under way will help determine how valuable the test is in screening.

PSA is very useful in monitoring recurrent disease. After surgery or radiation, the PSA level should be undetectable (or near undetectable). A rise in PSA after treatment could mean the disease is coming back and that further treatment should be considered. The PSA can also be used to follow the response to treatment for more advanced disease. Another marker being studied for following prostate cancer is the prostate-specific membrane antigen (PSMA), although it's not yet clear how useful it will be.

Some prostate cancers do not cause abnormal blood PSA levels and do not respond well to hormone therapy turn out to have neuroendocrine features. Men with these cancers may have higher than normal levels of chromogranin A. These cancers are more likely to respond to certain chemotherapy drugs. prostatic acid phosphate (PAP) is an older, less sensitive marker, which is no longer used very much.

GASTRIC CANCER

No marker has been developed specifically for this cancer. Some other digestive cancer markers may be elevated, particularly CEA. If the CEA levels are elevated at the time of diagnoses, the levels can be followed while the cancer is being treated.

TESTICULAR CANCER

Tumor markers are very important in this cancer and are used by doctors to follow its course. The markers usually elevated in the blood of men with testicular cancer are human chorionic gonadotropin (HCG) and alpha fetoprotein (AFP). There are different kinds of testicular cancers and they differ in the level and kind of marker that is elevated.

Seminoma

About 10% of men with seminoma, a type of testicular cancer, will have elevated HCG. None will have elevated AFP.

Nonseminoma

More than half of men with early stage disease will have elevated HCG or AFP or both. The amount of the marker found in the blood does not necessarily help in predicting outcome. The markers will be elevated in most men with more advanced disease. HCG is almost always elevated and AFP is never elevated in choriocarcinoma, a subtype of nonseminoma. As with the other nonseminomas, the amount of the marker found in the blood does not necessarily help in predicting outcome. In contrast AFP, but not HCG, is elevated in another subtype known as yolk sac tumor or endodermal sinus tumor.

Advantages of using tumor markers

- Screening and early detection of cancer.
- Aid in the diagnosis of cancer
- Determine response to therapy
- Prognostic indicator of disease progression
- Indicate relapse during follow-up period

Disadvantages of using tumor markers

- Lack of reliability
- Proteins and/or modified proteins may vary among individuals, between cell types, and even within the same cell under different stimuli or different disease states. Hence, it is difficult to know which value obtained from an individual is accurate and what value in different patients indicates a problem
- Normal cells as well as cancer cells can produce most tumor markers
- Tumor markers are not always present in early-stage cancers
- Tumor markers can be present because of noncancerous conditions
- People with cancer may never have elevated tumor markers in their blood
- Even when tumor marker levels are high, they are not specific enough to confirm the presence of cancer.

LABORATORY TECHNIQUES TO DETECT TUMOR MARKERS

The following techniques aid in identification and characterization of potential biomarkers; diagnostic and prognostic as well as conceivable therapeutic targets.

- Enzyme Linked Immuno Sorbant Assay (ELISA)
- Mass Spectrometry
- Two dimensional polyacrylamide gel electrophoresis (2D- PAGE)
- Multidimensional Protein Identification (Mud PIT)
- Surface enhancer laser desorption ionisation time of flight mass spectrometry (SELDI)
- Matrix Assisted Laser Desorption/ Ionisation mass spectrometry (MALDI)

CONCLUSION

The future holds great promise for the field of tumor markers. With the advances in genomic and proteomic technology, human diseases will be classified based on molecular rather than morphological analysis.

This will occur through techniques such as laser capture micro-dissection for the procurement of tissues and cells, and by combining genomic and proteomic analysis. Early diagnosis of disease is possible by using unique gene or protein profiles consisting of multiple biomarkers. The analysis of panels of protein biomarkers may be performed by using traditional ELISA or antibody-based protein chips for parallel testing. Furthermore, there will be many more diagnostic tests generated as a result of genomic and proteomic discoveries.

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