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Review article:

Tumor markers - a diagnostic tool in solid cancers

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ABSTRACT:

Tumor markers are biochemical substances elaborated by cancer cells either due to the cause or the effect of malignant process. These markers paly an increasingly important role in cancer detection and management. These laboratory based tests are potentially useful in screening for early malignancy, aiding cancer diagnosis ,determining prognosis, surveillance following a curative procedure.

The markers can be normal endogenous products at a greater rate produced in cancer cells. They may be represent as intracellular substances or may be released into circulation and appear in serum. In clinical practice, it refer to a molecule that can be detected in plasma and body fluids .

Clinically useful markers include stool occult blood screening for early colorectal cancer, carcinoembryonic antigen in the management of patients in colorectal cancer, both alpha feto protein and beta HCG in the management of germ cell tumors, tumor associated antigen like CA125, CA19.9, CA15.3 for monitoring therapy in patients with ovarian, pancreatic and gastric carcinoma. Hormone receptors estrogen, progesterone and HER-2 for predicting response to hormone therapy and identification of patients likely to respond to Trastuzumab . Enzymes and isoenzymes like prostatic specific antigen , neuron specific enolase etc . Serum and tissue proteins like beta2 microglobulin , glial fibrillary acid protein etc are some of the useful tumor markers. Circulating tumor cells , microRNA's , long noncoding RNA's are recently discovered tumor markers.

Electronic search of research and original articles from journals, systematic review using Medline and Pubmed, searches from the back of the references. Articles published till 2019 are included in the search

KEY WORDS: Tumor markers, Malignant solid tumors

Background:

Solid tumor is an abnormal mass of tissue that usually does not contain cysts or liquid areas. Solid tumors may be benign or malignant. Tumor Markers comprise a wide spectrum of biomacromolecules synthesized in excess concentration by a wide variety of neoplastic cells. These are biochemical indicators of presence of a tumor.[(1)] The markers could be endogenous products of highly active metabolic malignant cells or the products of newly switched on genes, which remained unexpressed in early life or newly acquired antigens at cellular and sub-cellular levels. In clinical practice, it refers to a molecule that can be detected in plasma and body fluids.[(2)]Tumor markers are measurable biochemicals that are associated with a malignancy. These markers are either produced by tumor cells (tumor-derived) or by the body in response to tumor cell

(tumor-associated). They are typically substances that are released into the circulation and thus measured in the blood.[3,4] Tumor markers are not the primary modalities for cancer diagnosis rather they can be used as laboratory test to support the diagnosis.[1] Inspite of these limitations, many tumor markers have shown excellent clinical relevance in monitoring efficacy of different modes of therapies during entire course of illness in cancer patients. Additionally, determination of markers also helps in early detection of cancer recurrence and in prognostication. Awareness for cancer and related tumor markers providing great opportunities for improving the management of cancer patients by enhancing the efficiency of detection and efficacy of treatment.

Tumor markers can be broadly classified as

1. Oncofetal antigens
2. Tumor associated antigens
3. Hormones
4. Hormone receptors
5. Enzymes and Isoenzymes
6. Serum and tissue proteins
7. Other biomolecules

An ideal tumor marker theoretically should have the following criteria

1. It should be highly sensitive and specific .
2 It should have high positive and negative predictive value.
3 100% accuracy in differentiating between healthy individuals and tumor patients.
4 It should be able to differentiate between neoplastic and non-neoplastic disease and show positive correlation with tumor volume and extent.
5 It should predict early recurrence and have prognostic value.
6 It should be clinically sensitive i.e. detectable at early stage of tumor.
7 Its levels should be preceding the neoplastic process, so that it should be useful for screening early cancer.
8 It should be either a universal marker for all types of malignancies or specific to one type of malignancy.
9 It should be easily assayable and be able to indicate all changes in cancer patients receiving treatment.

Unfortunately none of the tumor markers reported to date have above ideal characteristics. It is not specific to single malignancy. Every tumor marker is specific to a group of malignancies or a single organ. Malignant process is known to elaborate a group of markers.[5] Depending on the malignant cell type, a single organ can elaborate many cancer markers .

ALPHA FETOPROTEIN (AFP)

AFP, a very popular and extensively studied Oncofetal antigen . Although abundant in fetal blood, its concentration in normal adults is below 15 ng/ml. Excess amount of serum AFP beyond 500 ng/ ml indicates underlying malignancy except in cases of pregnancies. Serum AFP measurement is of valuable clinical aid in diagnosis, prognosis and monitoring primary hepatocellular carcinoma [6,7], non-seminomatous testicular germ cell tumors [8], germ cell tumors of ovary [9] and extragonadal germ cell tumors [10].The serum AFP measurements may be useful as a sensitive marker system for the early

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detection of recurring hepatocellular carcinoma, even before the clinical symptoms are evident. The most well differentiated and highly anaplastic hepatomas do not produce AFP, as the AFP synthesis is associated with degree of liver cell differentiation. Very significant elevation of serum AFP is documented rarely in malignancies of gastrointestinal tract, pancreas, lungs, kidney, and breast etc [11-14]. Serial AFP estimations help in distinguishing nonmalignant and malignant conditions. The rapid rise in AFP indicates failure to respond to treatment and thereby indicating its usefulness in monitoring treatment. Serum AFP and □hCG both together are valuable markers for nonseminomatous germ cell tumor. Evaluation of AFP-secreting malignancies could be of relevance in assisting oncologists in searching the unknown primaries.

HUMAN CHORIONIC GONADOTROPIN (□HCG)

HCG is a marker of germ cell tumors and trophoblastic disease. The beta subunit determines the immunological and hormone specificity. HCG is synthesized by the synctiotrophoblasts of the placenta during pregnancy. The reference values in serum of healthy men and non-pregnant women are less than 5 IU /ml and post-menopausal women are less than 10 IU /ml . HCG is a marker of first choice for gonadal choriocarcinoma and extragonadal choriocarcinoma. In testicular tumors, the detection of HCG and AFP correlates with the histological findings. The biochemical recurrence precedes by 3 months before the patient has symptoms of metastases. The marker also helps in monitoring high-risk group of testicular tumors . High levels of □hCG indicate poor prognosis and frequent assays during therapy level correlated to the clinical response. Serum HCG levels are rarely elevated in nontrophoblastic tumors such as lung, breast, pancreas and bladder cancers .[15]

CARCINO-EMBRYONIC ANTIGEN (CEA)

Carcinoembryonic antigen (CEA) is produced by certain embryonic and adult tissues in addition to adenocarcinoma of the digestive organs. Useful in detection of local and metastatic cancer recurrence after initial resection of the primary colorectal tumor, through periodic postoperative analysis of CEA . Measuring biliary CEA levels in patients with primary colorectal lesions might permit detection of small, occult colorectal liver metastases earlier than is now possible through conventional methods .The results of clinical studies that CEA, although originally thought to be specific for digestive tract cancers, may also be elevated in other malignancies and in some nonmalignant disorders.. A persistent elevation in circulating CEA following treatment is strongly indicative of occult metastatic and / or residual disease. A persistently rising CEA value may be associated with progressive malignant disease and a poor therapeutic response. A declining CEA value is generally indicative of a favorable prognosis and a good response to treatment. Use of the CEA test as an adjunctive test in predicting prognosis and as a aid in the management of cancer patients has been widely accepted .[16-20]

PROSTATE SPECIFIC ANTIGEN (PSA)

Prostate cancer is the fifth leading cause of cancer-associated mortality among men worldwide[21] Screening for prostate cancer with serum prostate-specific antigen aims to detect prostate cancer at an early, intervenable stage amenable to curative treatment and reduction in overall and disease-specific mortality. For early detection of prostate cancer, the American Urological Association and Food and Drug Administration have recommended combined use of digital rectal examination and serum PSA estimation annually in all men at the age 50 years without any family history of cancer and at the age of 40 years with family history of prostate cancer. Several studies have demonstrated an association between BPH and mildly elevated serum PSA concentrations. PSA is synthesized in very low quantity by normal healthy prostate, in moderate quantity by hyperplastic prostate and in excess amount by the malignant prostate. The overlapping serum PSA concentrations

between patients of BPH and patients with early, organ confined prostate adenocarcinoma limits the ability of serum total PSA in detecting early prostate cancer in appreciable number of patients associated with gray zone serum PSA concentrations. Compared to free PSA, the PSA.ACT complex concentration in serum is reported to rise in adenocarcinoma prostate patients compared to benign diseases of prostate. Hence the clinical analysis of molecular forms of the PSA, the free PSA or free PSA/total PSA ratio becomes important to evaluate their role in differentiating BPH with early malignant disease of prostate, in particular the adenocarcinoma prostate.

PROSTATE ACID PHOSPHATASE (PAP)

Acid phosphatase activity is 200 times more abundant in prostate tissue than in any other tissue. Acid phosphatase prostatic fraction is useful only in staging apparently localized disease . Interest in acid phosphatase assays in serum as a measure of prostatic cancer staging has decreased with the availability of the more sensitive and specific PSA assay.

TUMOR ASSOCIATED ANTIGENS

Tumor associated antigens are defined by highly specific monoclonal antibodies produced against tumor tissue or cell lines of a histologically well-defined primary tumors.

CANCER ANTIGEN 125 (CA 125)

CA125 is the most extensively studied biomarker for possible use in the early detection of ovarian cancer, monitoring of disease, early prediction of outcome, tumor status after completion of therapy , as a risk marker , early detection of recurrence , diagnosis when used alone or in combination with other markers. However, there have also been reports of elevated levels of soluble CA125 in a number of other malignant conditions, such as breast cancer , mesothelioma , non-Hodgkin's lymphoma , gastric cancer , leiomyoma and leiomyosarcoma of gastrointestinal origin . CA125 levels have also been found elevated in benign conditions , such as endometriosis , pregnancy , ovulatory cycles , liver diseases and congestive heart failure , as well as in infectious disease such as tuberculosis. [22]

HUMAN EPIDIDYMIS PROTEIN 4

Human epididymis protein 4 (HE4), a precursor of human epididymis protein, has been proposed as a tumor marker for ovarian cancer. HE4 has diagnostic sensitivity similar to that of CA 125, but an increased diagnostic specificity in patients with gynecologic malignancies compared with those with a benign gynecologic disease . The major drawback of using CA 125 as an initial step in such a screening strategy is that up to 20% of ovarian cancers do not express the antigen. It is therefore necessary to combine CA 125 with new tumor markers that can provide better diagnostic efficiency. In ovarian carcinomas, but not in normal tissue, the HE4 protein is N-glycosylated and secreted into the extracellular environment. HE4 was not specific for ovarian cancer and abnormal concentrations of this tumor marker were also found in endometrial cancer, NSCLC, and primary liver cancer. It shows a better specificity than CA 125 in benign, nongynecologic, and gynecologic diseases, as well as in the differential diagnosis of ovarian cancer from other malignant nonovarian diseases. Renal failure is the most important source of false-positive results with HE4, and HE4 results in patients with creatinine concentrations higher than 1.3 mg/dL should be evaluated with caution. HE4 improves the utility of CA 125 as a tumor marker in ovarian cancer, and using both markers simultaneously increases the tumor marker sensitivity in ovarian cancer.[23]

SERUM CA 19-9

Pancreatic cancer is an aggressive tumor with a dismal prognosis, biomarkers that can detect tumor in its early stages . Serum

CA 19-9 level has no role in screening asymptomatic populations, and has a sensitivity and specificity of 79–81% and 82–90% respectively for the diagnosis of pancreatic cancer in symptomatic patients. Pre-operative CA 19-9 serum levels provide important prognostic information in pancreatic cancer patients, correlate with tumor stage and independently predict overall survival. An increasing postoperative CA 19-9 serum level or failure of the CA 19-9 serum levels to normalize post- operatively is associated with a poor prognosis and suggests residual disease or the presence of occult metastases, while a decline or normalization of the post-operative CA 19-9 serum level, is associated with improved survival. Non-specific expression in several benign and malignant diseases ,an increased false positive results in the presence of obstructive jaundice severely limit the universal applicability of serum CA 19-9 levels in pancreatic cancer management. [24]

CA 15-3

CA 15-3 is the most frequently used tumour marker in invasive breast cancer. CA 15-3 concentration >30 kU/l is associated with a poor prognosis and led to an analysis of cancer spread and the search for metastases. In the non metastatic patients, an initial CA 15-3 concentration >40 kU/l was found to be an independent factor associated with poor prognosis.[25]

CA 72-4

CA 72-4 antigen detected in fetal epithelium and also in serum of patients of various adenocarcinomas. CA 72-4 once emerged as the tumor marker of first choice for gastric carcinoma and is thereby superior to CA 19-9 and CEA . Hence, CA 72-4 was considered to be the multiple markers for epithelial cell derived tumors .[26]

CYTOKERATINS/ KERATINS

Keratins are the intermediate filament (IF)-forming proteins of epithelial cells. In cancer, keratins are extensively used as diagnostic tumor markers, as epithelial malignancies largely maintain the specific keratin patterns associated with their respective cells of origin. Keratins have long and extensively been used as immunohistochemical markers in diagnostic and prognostic tumor pathology . Most adenocarcinomas express the simple epithelial keratins K8, K18 and K19, whereas K7 and K20 expression is variable. Squamous cell carcinomas are characterized by the expression of the stratified epithelial keratins K5, K14 and K17 and the hyperproliferative keratinocyte-type keratins K6 and K16 , K1/K10 may also be focally expressed, and K4 and K13 to a lesser extent.[27]

CYFRA 21-1

Serum CYFRA 21–1 is one of the most important serum markers in the diagnosis and prognosis of non-small cell lung cancer, especially squamous-cell carcinoma. Serum CYFRA 21–1 levels serve as a prognostic factor in patients with recurrent NSCL receiving 3rd-line or later gefitinib therapy.[28]

CALCITONIN

Calcitonin is a tumour marker essential for the diagnosis and follow-up of medullary thyroid cancer. Minimal and mild elevations in serum calcitonin may be seen in C-Cells hyperplasia, renal failure, autoimmune thyroiditis, and hypercalcaemia. Elevated calcitonin levels may result from non thyroid neuroendocrine tumours. [29]

CATHEPSIN D

Cathepsin D levels are related to tumor size, tumor grade, tumor aggressiveness, incidence of metastasis, prognosis and a degree of chemoresistance in variety of solid tumors including breast cancer ,neuroblastoma, glioma, melanoma, endometrial and ovarian tumors, colorectal carcinoma, head and neck tumors, pancreatic tumors, lung carcinoma, liver tumors, bladder

carcinoma, prostate tumors and gastric carcinoma .[30]

CHROMOGRANIN A

Chrogranin A measurement is useful laboratory tool for the diagnosis and follow-up of patients with neuroendocrine tumors . The highest mean values were observed in patients with carcinoid, pheochromocytoma, pancreatic/ gastrointestinal neuroendocrine tumors and parathyroid adenoma.[31]

CIRCULATING TUMOR CELLS

Circulating tumor cells (CTCs) have shown promising potential as liquid biopsies that facilitate early detection, prognosis, therapeutic target selection and monitoring treatment response in cancer patients. CTCs are described as cells shed by a primary tumor into vasculature and they keep circulating in the blood stream of cancer patients. One of the most axiomatic implications of CTCs is that they are minimally invasive indicators . Analysis of CTCs . can save a patient from worsening the condition with unsuitable medications. Furthermore, the earlier they are detected, faster and better treatment options can be made available to the patient. It provides the basis of understanding mutations and genotypic changes of malignant cells and hence provides the best suitable targeted therapy. They are potentially an alternative to invasive biopsies for detection, characterization and monitoring solid tumors. CTCs are not continuously shed in the circulation. They are discontinuous and might not be present in homogenous condition. Thus, while isolating CTCs a single blood sample might fall insufficient or may give inaccurate results. CTCs can be detected in almost all of the solid tumor malignancies and changes in the disease state can be predicted with the help of CTCs .[32]

CIRCULATING MICRORNA

MicroRNAs are endogenous single-stranded non-coding small RNA molecules that can be secreted into the circulation and exist stably. They usually exhibit aberrant expression under different physiological and pathological conditions. Recently, differentially expressed circulating microRNAs were focused on as potential biomarkers for cancer screening. They could be optimal to determine tumor sub- type and pathology, contributing to the selection for a more efficient therapeutic approach. miR-181-5p, miR-361- 5p, and miR-320b were significantly elevated in plasma exosomes of NSCLC patients. The levels of miR-181-5p and miR-361-5p were increased by more than 10 times in adenocarcinoma patients than squamous cell carcinoma patients, and miR-320b in SCC samples increased by over 10 times than in ADC ones. miR-30a-3p and miR-30e-3p were specifically downregulated in ADC patients, while miR-10b-5p and miR-15b-5p were decreased in SCC patients. Therefore, investigators suggest that these miRNA panels may be not only applicable in NSCLC diagnosis, but also helpful to subtype discrimination. Circulating miRNAs were found to be associated with clinical tumor stage and/or metastasis. In osteosarcoma patients, miR-497-5p was significantly downregulated in primary tumor tissues, metastatic tissues, and serum compared to healthy controls . The disadvantage and limitation of circulating miRNAs as diagnosis and prognosis biomarkers is because of the diversified origin of circulating miRNAs influences the effectiveness partially[1]. Most of potential miRNA biomarkers ubiquitously exist in both healthy individuals and cancer patients. The differences in their expression levels between healthy people and patients are usually quite tiny. So the way of sampling cannot be ignored to distinguish cancers from healthy state or other benign injury .[33]

LONG NONCODING RNAS

lncRNAs, comprising more than 200 nucleotides, are involved in a wide range of biological processes and diseases including cancer development and metastasis, even though they lack an open reading frame .[34]

lncRNAs are recently discovered noncoding endogenous RNAs that critically regulates the development, invasion, and metastasis of cancer cells. They are dysregulated in different types of malignancies and have the potential to serve as diagnostic markers for cancer. The expression of noncoding RNAs is altered following many diseases, and besides, some of them can be secreted from the cells into the circulation following the apoptotic and necrotic cell death. These secreted noncoding RNAs are known as cell free RNA. These RNAs can be secreted from the cell through the apoptotic body, extracellular vesicles including microvesicle and exosome, and bind to proteins. Since, lncRNAs display high organ and cell specificity, can be found in the blood, urine, tumor tissue, or other tissues or bodily fluids. lncRNAs are used as biomarkers for diagnosis, prognosis, and therapy[35]

CONCLUSION

Serem tumor markers are firmly entrenched as one of the primary tools in an oncologists armamentarium. They are used in a broad range of applications from diagnostic assistance , assessing prognosis or guiding therapeutic decisions.

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