Serum Tumor Markers: Diagnostic or Para-Diagnostic

Pages with reference to book, From 118 To 120
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Tumour marker is a molecular moiety; the presence, the absence, or a quantitative change in its status marks the presence or absence of a malignant disease or a change in tumour burden. They are of interest being raw material of refined diagnosis and rational therapy. Historically Bence-Jones Proteins were the first one reliably described by Bence-Jones in 1846, followed by Intestinal cancer specific antigens by Witebsky and Hirzfeld in 1929, human chorionic gonadotrophinby Zondek in 1930, prostatic acid phosphatase in 1933 by Gutmann and Gutmann, and Alpha fetoprotein by Abelev in 1963[1].

A sero/circulating tumour marker ideally facilitates primaiy detection, assists in monitoring, helps early detection of recurrence, predicting tumor response, assists in patient selection for adjuvant treatment, helps in localization of a metastasis and serves as a guide in assessing prognosis[2]. An ideal tumor marker should be easily and inexpensively evaluable, should be secreted into body fluids rather than cell or tissue bound only, tumor specific, should have an stoichiometric relationship with tumor cell mass and extent, should be at significant level of detection very early in disease, should have stable (not wildly fluctuating) body fluid levels, should have proportionate relation with clinical stage, prognosticate recurrence risk, varies in parallel with tumor status over a time period, reflect current disease status and precede a clinical recurrence[1,2].

A tumor marker physiologically can be an antigen, hormone, an enzyme, a co-enzyme, growth factor, oncogene, proto-oncogene, tumor activation gene, tumor suppressor gene, or a cell receptor. It can biochemically be a protein, a mutant protein, lipoprotein, glycoprotein, glycolipid, viral proteins, proteoglycan, polysaccharide, lipid, ganglioside, sialomucin, fibronectin, or nucleic acid[3-9].

Tumor markers are extensively and increasingly being used in sero-screening, radio localization (radio-immuno-diagnosis, immuno-scintigraphy), immuno-cytochemical diagnosis, sub-typing of hematologic malignancies and Iymphomas, in situ hybridization, genetic fingerprinting (DNA probes) and polymerase chain reaction (PCR). The therapeutic exploitation of tumor markers are also innumerable viz bone marrow clearance and transplantation. tumor targeting, anti-idiotype antibodies and monoclonals. Tumor markers are of immense value in monitoring treatment, detecting recurrence, finding out the tissue of origin in MUO (Metastasis ofunknow origin)and predicting prognosis[10-12].

The limitations of tumor marker usage are lack of absolute specificity, high cost and dynamic antigenic make up (masking, change in epitope configuration) and rather unparallel changes with treatment. Most of the tumor markers are products of differentiated tumor cells and thus their serum levels are inversely proportional to anaplastic grade making their reliability questionable in anaplastic tumors or in tumor which progress to a higher anaplastic grade[13,14].

With more and more insight into monitoring malignant growths with the help of tumor markers. it is now clear that not only the density (serum level of tumor maker), but velocity (speed of rise over a given time) and ratio of free and bound marker molecule which are important determinants of pathophysiology of malignant process.

The list of tumor markers is exponentially increasing with time with more and more impetus in clinical research, screening and monitoring. Some of these important ones include from AFP (aiphafetoproteinin primaiy hepatocellular carcinoma, germ cell tumours of testis/ovary). HCG (human chorionic gonadotrophin in trophoblastic tumours), CEA (carcinoembryonic antigen in colon, stomach, pancreas, gall bladder tumours), beta 1 antitrypsin (hepatocellular carcinoma), collagen, laminin (sarcomas), vimentin (sarcoma, renal cell carcinoma, lymphoma. leukemia, melanoma), cytokeratin

(sarcoma, carcinoma), NSE (neuron specific enolase in variety of neurological turnours), S-100 protein (melanoma, sarcoma, histiocytoma), PSA (prostate specific antigen in prostatic carcinoma), EMA (epithelial membrane antigen in urinary bladder turnours). Desmin (sarcoma and uterine tumours), chrornogranin (neuroendocrine tumours like pheochromocytoma, carcinoid), factor VIII, CD3 1, CD34 (vascular sarcoma), HPL (human placental lactogen (placental site tumours), LCA (leucocyte common antigen in leukemia, lymphoma, histiocytic tumours), Gross cystic disease fluid protein-15 (breast carcinoma), Inolucrin (Squamous cell carcinoma), lymphoid cell epitopes and activation markers (lymphoma and leukemia), immunoglobulins (myeloma), muramidase (mycloid leukemia), myoglobin (muscular sarcoma), NK1/C3 (nielanoma), thyroglobulin (thyroid cancer), pancreatic cancer antigen (pancreatic carcinoma), ER, PR, EGFR (estrogen receptor/progesterone receptor and epidermal growth facor receptor in breast, memngeal and gall bladder tumours), Leu-7 (leukemia, lymphorna), p53 (carcinoma), PIVKA2 (hepatocellular carcinoma), etc[15].

There are not man' tumor markers which fulfill the criteria of an ideal or absolute tumor marker. The ones which come closest to this are B-HCG, PSA, AFP and CA-125[16]. HCG have a linear relationship to choriocarcinoma cells, urinary and serum levels are in parallel; yet it is found also in pregnancy, ovarian tumors and hydatidiform benign mole. Failure to detect HCG does not exclude presence of choriocarcinoma. It is however, valuable in screening, monitoring, prognosis and treatment planning. The ratio of serum Vs CSF level is predictive ofceztbral metastasis[17]. AFP is elevated in testicular, ovarian, bronchial, gastric, pancreatic tumors and liver cirrhosis; in addition to primary liver cattinoma (HCC).It is raised in 60-90% cases and its relation with HCC is more significant in black race. Smalitumors and anaplastic tumors may show a normal AFP level. Ultrasonography has a superior diagnostic sensitivity than AFP. It may be helpful in assessing treatment response or drug resistance mandating alternative treatment[18,19]. PSA has a sensitivity of 57-79%, sensitivity 59-68%, a positive predictive value upto 49% and a detection rate upto 2.6%[20,21]. It is increased in BPH, prostatitis and after uretheric cathetenzation/prostatic manipulation as well; being 'prostate specific' rather than 'prostate cancer specific'. The normal values of PSA are <5.0, a patient value between 5-10 indicate a 15-20% chance of a prostatic cancer, while a value >10 carries a chance >65%. PSA sensitivity and specificity can be improved by incorporating PSA density, age-specific reference ranges, PSA velocity and by measuring free, total, complexed PSA values[22-25]. CA-125 is elevated in 80% women having ovarian carcinoma but it is also elevated in benign cysts, ascites and chronic pelvic orsystemic infections. Its value also varies with different phases of menstrual cycle. It has a reasonable prognostic and predictive value, but specificity is not reasonable enough to be used as a screening test[26-31].

Tumour markers no doubt have revolutionised our understanding of the malignant process and its pathobiology. They are of immense value in diagnosis of malignant process, at places absolutely diagnostic. Serum or body fluid levels of these tumour markers are a great ancillary support in diagnostic oncology. Their serum values however, have definate limitations and there is no ideal marker yet available. Many a times not one suffice and a battery of multiple tumour markers is required to be assayed which is rather expensive to be carried out in a developing country. They should be treated with respect, not to be taken as 'diagnostic' but as 'an aid to diagnosis'; going parallel yet hand in hand to clinical evaluation and judgemeñt and should be interpreted as such. Their more significant and invaluable exploitation is in prognosis prediction and monitoring relapse and yet not many clinicians would like to embark upon treatment with a serological relapse unless it is supplemented by clinical evaluation and/or other investigational evidence. Serum tumour markers are thus just like ones own shadow; always related and associated, but only for a brief time in twenty four hours exactly equal to your own.

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