Students' Corner
Review Article

Chromogranin A — Serum marker for prostate cancer

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Abstract

Prostate Cancer is the second most prevalent neoplasm after lung cancer in men. It commonly presents in patients with a strong family history. The measurement of Prostate Specific Antigen (PSA) in free and bound forms is one of the methods to diagnose it. It is very much useful for monitoring the therapeutic efficacy, staging, prognosis, tumour volume evaluation, detection of recurrent disease, screening and early diagnosis. Chromogranin A (CgA) is an acidic glycoprotein that is commonly expressed by neuroendocrine cells and constitutes one of the most profuse components of secretory granules. When a tumour develops in an endocrine tissue, it becomes the main source of circulating CgA. Its concentration is thought to be elevated in relation to neuroendocrine differentiation of prostate cancer. CgA is a useful predictive marker in patients with prostatic cancer who have lower PSA. It is known that neuroendocrine cells in the prostate do not contain androgen receptors and are not regulated by androgens. PSA expression was stimulated by androgen through androgen receptors, so it is suggested that cases of prostate cancer associated with low serum PSA and high serum CgA, which would have more neuroendocrine cells with less androgen receptors, may show resistance to endocrine therapy and a poor prognosis. Therefore serum CgA tends to be elevated in high grade prostate cancer cases. Hence it can be used to fill the gap if any left by PSA when combined with serum PSA, the serum marker may effectively predict the prognosis after endocrine therapy. CgA expression in prostate cancer biopsies is an independent extrapolative factor of hormone refractory disease in patients with newly diagnosed prostate cancer on early androgen deprivation therapy.

Introduction

Prostate cancer is the most common noncutaneous cancer among males.[1] It constitutes about 10% of diagnosed cancers.[1] More than 1 million new cases of cancer are diagnosed annually in America: prostate cancer, with a prevalence of 19%, comes second after lung cancer as the most widespread malignancy in men.[2] Prostate cancer is uncommon in men younger than 50 and is rarely diagnosed in men younger than 40 years.[1] The diagnosis and treatment of prostate cancer has continued to advance. Due to the development of prostate-specific antigen (PSA) screening, prostate cancer is now being diagnosed earlier.[1] Furthermore, according to the US Surveillance, Epidemiology and End Results (SEER) program, the 5 year survival rate for Prostate Cancer was 75% from 1983 to 1985, and 99% from 1995 to 2000 - the utmost enhancement for any tumour.[3] It is possible that screening is responsible for decreasing prostate cancer- specific mortality in the US.[3] Similar results occurred when PSA testing was made freely available in Tyrol, Austria.[3] The prostate cancer mortality declined at a significantly faster rate in Tyrol than in the remainder of Austria, where screening was then not as widely used.[3] Although prostate cancer can be a slow-growing cancer, thousands of men die of the disease each year.[1] The prevalence of prostate Cancer is low in Pakistan, with a figure of 3.8% of the male population.[4] Gene alterations on chromosome 1, 17, and the X chromosome have been found in some patients with a family history of prostate cancer.[1] The hereditary prostate cancer 1 (HPC1) gene and the predisposing for cancer of the prostate (PCAP) gene is on chromosome 1.[1] As prostate cancer is one of the leading causes of death worldwide, continuous advances have provided a new understanding of the diagnosis, staging, and treatment of metastatic and advanced prostate cancer. The earlier definition of advanced disease, in which patients presented with bone metastasis and soft tissue involvement, has improved in recent years.[5] It is estimated that 1 in 10 men will develop prostate cancer in their lifetime.[5] Because of its genetic linkage, prostate cancer is more common in patients with a strong family history.[5] Also, people who smoke, African American males, and patients who consume a diet high in animal fat or high in chromium have increased risk of the neoplasm.[5]

The measurement of PSA in free and bound forms is one of the methods to diagnose prostate cancer. The lower the ratio of free-to-total PSA, the higher the likelihood of cancer.[1] DRE and PSA evaluation are the 2 components necessary for a contemporary screening programme. Transrectal ultrasonography (TRUS) has been associated with a high false-positive rate, making it unsuitable as a screening tool.[1] The American Cancer Society recommends that both PSA evaluation and DRE should be offered annually, beginning at age 50 years, to men who have at least a 10-year life expectancy and to high-risk younger men.[1] Regarding potential risks and benefits of intervention, information

should be provided to patients. Serum Prostatic Acid Phosphatase has also been used as a tumour marker for diagnosis, staging and monitoring of prostate cancer for many years. But due to the introduction of Prostate Specific Antigen (PSA), the position of Phosphatic Acid Phosphatase (PAP) is not clear. In a study conducted at Department of Radiotherapy and Oncology, Punjab Medical College/Allied Hospital-Faisalabad, it was seen regardless of measurement of PAP and PSA the results showed that not any of the patients with metastatic prostate cancer had normal PSA and raised PAP. So there is no clinical benefit of concurrent fortitude of both the tumour markers. In fact there were some patients who had an elevated PSA with normal PAP.[5]

It is also seen that hypocalcaemia is an uncommon but a well renowned facet of prostate cancer and bone metastasis. The mechanism of hypocalcaemia appears to be excessive uptake of calcium by the osteoblastic metastasis. Therefore calcium levels should be checked in all patients with prostate cancer and metastatic bone disease as this may have an effect on their symptoms and the use of bisphosphonate therapy.[6]

Use of PSA as a serum marker:

PSA is now recognized as the leading tumour marker for prostate cancer. Wang et al. reported PSA in the prostate in 1977 and characterized the protein definitively in 1979.[7] PSA was purified from both prostatic tissue and seminal plasma. PSA's unique tissue specificity is what makes it significant as a tumour marker. A single polypeptide, PSA occurs both in normal and malignant prostatic tissue and in the glands of men with Benign Prostatic Hyperplasia (BPH), but not in any other human tissue.[7] PSA is very valuable as a tumour marker for prostatic cancer and is used for monitoring therapeutic usefulness, staging, prognosis, tumour volume evaluation, detection of recurrent disease, confirmation of tissue of prostatic origin, screening and diagnosis.

The FDA has approved serum PSA for use as a prostate cancer screening laboratory test. Akin to other serum tumour markers, it is made by both normal and neoplastic glands. In men with prostate cancer, the serum levels can be elevated in both localized and advanced or disseminate disease.[7] Elevated serum PSA concentrations have been reported in patients with prostate cancer, as well as in benign prostatic hyperplasia (BPH) and prostatitis, leading to a huge percentage of false positive screening results.[8] However, values above the normal range 0-4 ng/ml are one of the earliest signs of prostate cancer, allowing diagnosis in many cases while the cancer is still curbed to the gland.[8] Serum PSA values >20 ng/ml are sturdily pinpointing of prostate cancer. Nonetheless, values in the intermediate range 4-20 ng/ml represent a diagnostic 'gray zone' i.e. predilection to prostate cancer, in which differentiation between benign and malignant enlargement poses a predicament.[8]

Total PSA increases with age and prostate mass, therefore, BPH and Prostate Cancer cases show higher levels of PSA. The problem, conversely, is that in the initial stages of Prostate Cancer when the prostatic growth is in the initial stages the total PSA does amplify but delineation between BPH and Prostate Cancer is not apparent. Consequently PSA is a valuable marker for early on detection of prostate cancer.[8] PSA is very noteworthy in diagnosis of prostate cancer when it is high. But its significance in cancer detection is decreased when serum PSA level is low i.e. 2.5-10ng/ml.[9] Prostate specific antigen occurs in different molecular forms. Most of serum PSA complexes with serum protein inhibitor i.e. 70-90% are bound with alpha 1 antichymotrypsin.[10] Unbound form is called free prostate specific antigen (FPSA). Nowadays more patients are undergoing prostate biopsy on the basis of serum PSA testing. Therefore in a research, the authors assessed the ability of fPSA/tPSA ratio to total PSA in detection of prostate cancer.[10]

Chromogranin A: Utility in Neuroendocrine Tumours?

Chromogranin A (CgA) is an acidic glycoprotein with a molecular mass of 49 kd that is extensively expressed by neuroendocrine cells and constitutes one of the most plentiful components of secretory granules.[1] CgA is physiologically released by exocytosis and can be found in blood. In particular, when a tumour develops in an endocrine tissue, it becomes the main source of circulating CgA.[2,3] High CgA levels have been established in the serum or plasma of patients with dissimilar types of endocrine tumours such as medullary thyroid carcinoma, pheochromocytoma, and enterochromaffin and pancreatic islet cell tumours.[11]

Recent studies designate that circulating CgA levels associate definitely with an enterochromaffin like (ECL) cell mass in patients with autoimmune chronic atrophic gastritis,[9,12] gastrinoma, and multiple endocrine neoplasia syndrome type 17,[10] who may develop potentially malignant gastric carcinoids.[11] CgA can have clinical applications in nonfunctioning neuroendocrine tumours that are either not able to secrete hormonal products or release products which cannot be detected by current techniques.[13]

Chromogranin A concentration as a serum marker to predict prognosis after endocrine therapy for prostate cancer:

CgA is in getting recognition as a serum marker of neuroendocrine tumours as explained above and the concentration is considered to be elevated with regard to neuroendocrine differentiation of prostate cancer. Immunohistological evaluation has revealed neuroendocrine markers in prostatic carcinoma, including neuron specific enolase, Chromogranin A, calcitonin, pancreastatin, parathyroid

hormone, synaptophysin, serotonin, somatostatin, adrenocorticotropic hormone and thyroid stimulating hormone.[12] Out of these markers CgA is generally expressed in neuroendocrine prostatic carcinoma.[12]

Due to better measuring techniques it has become simpler to measure serum or plasma CgA and the results have become more reliable. Other authors have reported that CgA should be used as a marker for neuroendocrine differentiation and an early elevated serum level indicates resistance to hormone therapy.[13]

It was noted that 91% of prostate glands had neuroendocrine cells and patients with CgA positive tumour cells had elevated serum CgA, although immunohistological findings and serum levels of other neuroendocrine markers described above suggest that CgA should be a useful marker for predicting the extent of neuroendocrine differentiation in prostatic tumours.[12]

CgA is a useful prognostic marker in patients with prostatic cancer who have lower PSA.[12] It is known that neuroendocrine cells in the prostate do not contain androgen receptors and are not regulated by androgen. PSA expression was stimulated by androgen through androgen receptors.[12] Therefore, it is suggested that cases of prostate cancer related to low serum PSA and high serum CgA, which would have more neuroendocrine cells with less androgen receptors, may show resistance to endocrine therapy and a poor prognosis.[12] Therefore serum CgA tends to be elevated in high grade prostate cancer cases. Hence it can be used to seal the break if any left by PSA[12] when joined with serum PSA, the serum marker may successfully envisage the prediction after endocrine therapy.[12]

In men with prostate cancer, elevated CgA levels are associated with high grade disease, according to a report.[14] When combined with PSA measurements, these levels could be helpful in predicting prognosis after endocrine therapy.[14] In a research the predictive value of serum CgA levels was assessed in 108 prostate cancer patients and in 66 men with benign prostatic hyperplasia.[14] After CgA determination, the cancer patients received endocrine therapy.[14] It was noted that the average CgA concentration in both groups of men was similar, suggesting that no union exists between elevated CgA levels with Benign prostatic hyperplasia and prostatic carcinoma.[14]

Among men with cancer, however, those with poorly-differentiated disease had significantly higher levels (45.3 ng/mL) than those with well-differentiated disease (72.5 ng/mL, $p = 0.044$).[14] In patients with stage D disease, survival was significantly lower in patients with CgA levels above the median level of 49.7 ng/mL than in those with lower levels. However, when PSA levels exceeded 172.1ng/mL, the CgA level had no demeanor on prognosis. These findings show that cases of prostate cancer which are coupled with low serum PSA and high serum CgA may show resistance to endocrine therapy and for this reason a pitiable prognosis.[14]

In a research, serum CgA values were determined by monoclonal immunoradiometric assay in 108 patients with prostate cancer before treatment and in 66 with benign prostatic hyperplasia. In those with prostate cancer clinicopathological parameters, the response to endocrine therapy and the prognosis were evaluated in relation to serum CgA. It was decided that serum CgA tends to be elevated in patients with high grade prostate cancer.[15]

In a study, researchers evaluated serum CgA as a neuroendocrine marker throughout endocrine therapy. The patients' survivals were not related to pretreatment CgA values, which can be explained by moderately higher PSA values before endocrine therapy. It was found that CgA values did not have association with PSA values. In addition, CgA values increased constantly during endocrine therapy in spite of PSA response. Therefore during endocrine therapy in metastatic prostate cancer patients, serum CgA values were not related to serum PSA levels, and increased as treatment periods increased. It is recommended that CgA rapidity has the prospective to foresee recurrence and androgen independency after endocrine therapy.[16]

Conclusion

CgA expression in prostate cancer biopsies is an autonomous prognostic factor of hormone intractable disease in patients with recently diagnosed prostate cancer on early androgen deprivation therapy. Plasma CgA is also an unswerving predictive marker and the prognostic importance is maintained over time.

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