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Article : Serum Interleukin-18 levels at a base line could serve as a better differentiating factor for carcinoma prostate and benign prostate hyperplasia –A study in north Indian population

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Abstract :

Aim: To explore the role of serum interleukin -18 (IL-18) levels and its significance in prostate carcinoma patients.

Method: 90 subjects were enrolled during June 2010 to May 2011 after Institutional ethical approval, 44 biopsy proven prostate cancer patients and age matched independent 46 benign prostate hyperplasia (BPH) patients as controls with in age group of 40-80 years. The Serum PSA level, interleukin-18 levels were measured by enzyme linked immunosorbent assay (ELISA) and significance of difference between various group was compared by using ANOVA analysis.

Results

The mean IL-18 of carcinoma prostate group was found to be significantly ($p<0.01$) higher than BPH group. It also showed its increase value in patient with its advanced stages.

Conclusions

These findings demonstrate that serum IL-18 may be used as an useful independent diagnostic biomarker in patient with prostate carcinoma but still more study on larger sample size is needed for its validation.

Introduction

World-wide, prostate cancer is one of the commonest cancers in men. Currently, serum prostate specific antigen (PSA) is considered the best tumor marker for detecting early cancer and it also has prognostic value. However, there are certain drawbacks of PSA. The most important drawback is that it is prostate-specific and not cancer-specific. The serum levels of PSA rise in many conditions like benign enlargement and prostatitis. There is an ever-growing research for newer markers that can give better diagnostic and prognostic information.

With better understanding of the molecular mechanisms of carcinogenesis many newer molecules are being evaluated by researchers that are better than PSA. Various interleukins participate in the steps of prostate carcinogenesis

Interleukin-18 (IL-18), formerly called interferon-gamma-inducing factor, is a recently discovered cytokine that plays an important role in the Th1 response. IL-18 is mainly produced by activated macrophages that are able to induce interferon-gamma (IFN-γ) and tumor necrosis factor-α, as well as enhancing the cytotoxicity of NK cells and FasL expression [1-3]**.** Recent results show that even prostate tumor cells could secrete IL-18 in response to IFN-γ and that IL-18 could act as an autocrine/paracrine factor for the tumor [4]**.** The purpose of this study was to investigate the possible role of serum IL-18 as a diagnostic marker for cancer prostate.

Methods

Between June 2010 and May 2011, 90 men who agreed to participate in this study, after obtaining the Institutional Ethical clearance. The recruited Fourty Four men with histologically proven cancer prostate (Group 1) and Fourty Six benign prostatic hyperplasia (BPH) (Group 2) as control. These Group 2 men were symptomatic had serum PSA less than 4 and failed in biopsy approval. Men having diabetes, arthritis, cardiovascular disease, hepatitis, AIDS and other inflammatory diseases were excluded.

Immediately after blood sampling, serum was obtained by centrifugation at 2000 r/min for 15 min at 4^{o}C and stored at -80 ^{o}C until later analysis. Serum PSA, and IL-18 (Bender Med Systems, ELISA kits Vienna, Austria) levels were determined using ELISA kits as per standard protocol of manufacturers.

Statistical analysis

Groups were compared by one way analysis of variance (ANOVA) and the significance of mean difference between the groups was done by Newman-Keuls post-hoc test. Survival among groups was compared by Logrank test. A two-tailed (α=2) probability (p) value less than 0.05 ($p<0.05$) was considered to be statistically significant.

Results

The mean ages for cancer and benign prostate hyperplasia were 69.3±4.3, 68.9±5.36, years respectively. The levels of prostate serum antigen and interleukin-18 summarized in Table 1. Table 1 shows that as Tumor-stage progresses the levels of PSA and IL-18 increases. In this study, on comparing (BPH, T2, T3 and T4) groups together, the mean PSA in all TNM stages were significantly ($p<0.01$) higher than BPH groups. However, the mean PSA in all TNM stages did not differed significantly ($p>0.05$) i.e. found to be statistically the same. In contrast, the mean IL-18 of all TNM stages also higher significantly ($p<0.01$) than BPH groups. Further, the level of it in both TNM stage T3 and T4 was also found significantly ($p<0.01$) high than the TNM stage T2. Furthermore, the mean IL-18 of TNM stage T4 was also significantly ($p<0.01$) higher than the TNM stage T3.

Table 1 -

Table 1. Summary (Mean ± SE) of carcinoma prostate markers in five groups of subjects

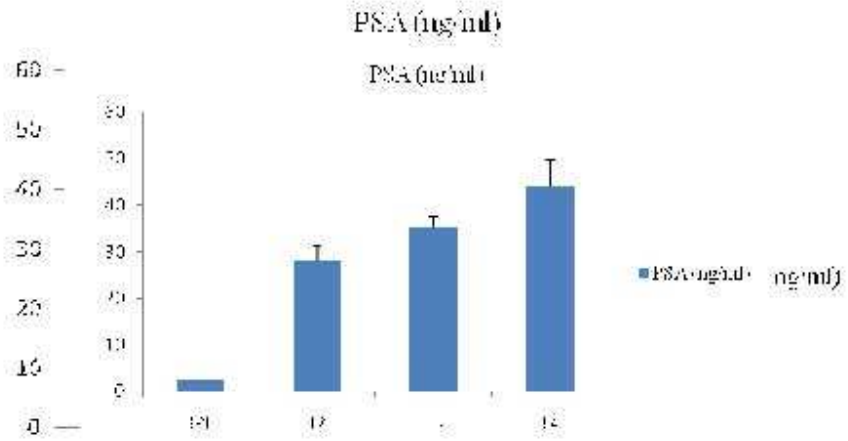
Variables	BPH (n=46)	Carcinoma prostate (n=44)		
		T2 (n=11)	T3 (n=16)	T4 (n=17)
PSA (ng/ml)	2.32 ± 0.14	27.93 ± 3.25[b]	35.11 ± 2.36[b]	44.30 ± 5.29[b]

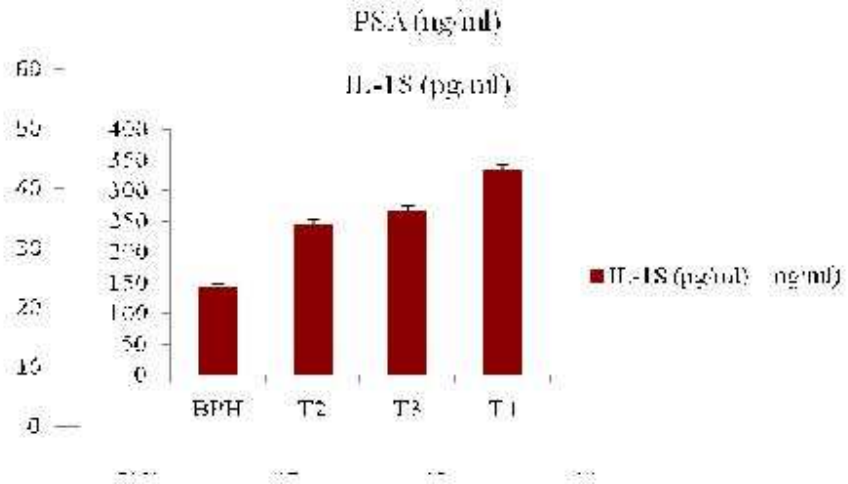
Interleukin-18 (pg/ml)	145.88 ± 1.93	243.42 ± 9.48[b]	268.74 ± 6.28[bc]	333.75 ± 7.86[bcd]

[b]p<0.01- in comparison with BPH

[c]p<0.01- in comparison with T2

[d]p<0.01- in comparison with T3





Discussion

The present study examined the level of serum IL-18 in various stages of carcinoma with BPH and tried to correlate them as a better differentiating factor for BPH with progression of carcinoma. The IL-18 is well known for its biological activities *via* its capacity of stimulating innate immunity and both Th1 and Th2-mediated responses. Few study also depicted its anti-tumor effects that are mediated by enhancement of NK cell activity, reduction of tumorigenesis, induction of apoptosis and inhibition of angiogenesis in tumor cells [5] Moreover few study data suggest that an inappropriate production of IL-18 contributes to the pathogenesis of cancers and may influence the clinical outcome of patients [6]

This study result showed that the levels of serum IL-18 are significantly elevated in prostate cancer patients compared with benign prostate hyperplasia patients and also its expression in different stage of carcinoma, single earlier study in Chinese population by**Shaojun Nong et al** showed increase in trends but they reported quite high expression of serum level and they compare the carcinoma patient with twenty five healthy volunteer as controls [7],although appearance of this cancer is in old age and no relation with benign prostate hyperplasia was given. Comparing all four (BPH, T2, T3 and T4) groups together, the mean PSA in all TNM stages were significantly ($p<0.01$) higher than BPH groups. In contrast, the mean IL-18 of all TNM stages also higher significantly ($p<0.01$) than BPH groups. Thus increase levels of IL-18 expression has been seen in all stages as they progresses .The pathways for IL-18 production and its mechanisms for anti tumor effect is documented but its clear mode of action in patients with prostate carcinoma remain to be determined.Its higher expression is reported in various carcinoma as gastric [8]**,** breast [9]and also from colonic [10]**.** Our results were similar to these findings.

Thus in current study it was seen that the expression of pro-inflammatory (IL-18) values are higher. Few study demonstrated that the bioactive IL-18 is most likely produced by the adjacent normal cells **.**Thus it can be presumed that IL-18 production by the normal adjacent prostate cells may be defense response mechanism against tumor growth and spread of prostate carcinoma [11]**.**

It was suggested that up regulation of IL-18 secretion may reflect the influence of prostate tumors on the systemic immune response. It is believed that this strategy helps the tumor cells to escape from host-immune surveillance and may account

for the fact that serum IL-18 level is high in patient with progression of stage. This higher concentration in patients with prostate cancer may reflect the degree of defense mechanism against tumor growth and metastasis.

Conclusions

In conclusion, our data demonstrate that serum IL-18 levels increases as stages progresses from bph to carcinoma so it may help in management of patient and proved to be useful biological markers for clinical differentiation in patients with prostate cancer and BPH. IL-18 could serve as better immunostimulating agent, thus body immune system may surmount an effective response against treating drug and carcinoma. Thus, more study on larger sample is needed so the detailed role of IL-18 in prostate cancer may be elucidated and role of immune player involved in tumor progression can be understand and thus a potent accurate biomarker can be developed .

List of Abbreviations

IL-Interleukin, TNF- Tumor Necrosis Factor, DC-Dendritic Cells, TNM -Tumor Node Metastasis, BPH-Benign Prostate Hyperplasia,

Competing interests

The authors have no competing interests.

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