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Inflammatory Patterns in the Prostate Gland and Serum Cytokine Activities in Primary Adenocarcinoma of the Prostate in Port Harcourt, Nigeria

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Abstract

Introduction: Chronic inflammation and pro-inflammatory cytokines such as (1L-6 and TNF-α) have been implicated in prostate carcinogenesis and metastasis. This study aims to evaluate serum concentrations of IL-6 and TNF-α, and to determine their association with clinicopathological patterns of prostate cancer in affected patients.

Materials and Methods: Ninety (90) patients with histologically diagnosed prostate cancer (PCa), treated at the Urology Division of the University of Port Harcourt Teaching Hospital (UPTH), Nigeria were involved in this study. The enzyme-linked immunosorbent assay (ELISA) technique was used to assay cytokines (IL-6 and TNF-α), and serum PSA. Gleason Scores were categorized as well differentiated (GS of ≤ 6), moderately differentiated (GS = 7), and poorly differentiated (GS 8-10). Results were analyzed with IBM SPSS version 20.0. Pearson's correlation test was used to determine the correlation between the cytokines (IL-6 and TNF-α) and Gleason Scores.

Results: The modal age group with PCa was 60-69 years. The mean age of patients was 68.78±8.26 years, and the mean serum PSA 93.24 ± 78pg/ml. Serum levels of IL-6 and TNF-α were 8.0pg/ml, 11.2pg/ml and (27.0 ± 26.4pg/ml) respectively. Forty-six subjects had poorly differentiated PCa (GS 8-10); 17 moderately differentiated (GS 7); and 27 well differentiated (GS ≤ 6). Mean serum levels of IL-6, TNF-α and PSA (113.1ng/ml) were raised and found highest in those with poorly differentiated PCa.

Conclusion: The observed correlation was positive but weak. The patients might have commenced undeclared anti-inflammatory drugs that depressed inflammation. However, a larger sample size would probably confirm the prognostic value of IL-6 and TNF-α in PCa subjects.

Keywords: Inflammatory patterns in the prostate; Primary adenocarcinoma of the prostate; Serum cytokine activities; Prostate cancer patients; Port Harcourt; Nigeria

1. Introduction

Prostate cancer (PCa) is a very common disease in middle-aged and elderly men with high morbidity and mortality globally. It was found the second most commonly diagnosed cancer (apart from non-melanoma skin cancer), and the fifth leading cause of cancer-related mortality in men globally in 2018 [1]. In 2018 GLOBOCAN estimates of PCa, 1,276,106 new cases were reported worldwide with a higher prevalence in the developed countries causing 358,989 deaths. These deaths constituted 3.8% of all deaths caused by cancer in men [2, 3]. Age is the strongest risk factor for

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PCa with a sharp rise after middle age [4]. Over 85% of newly diagnosed patients were above the age of 60 years [5,6,7]. In Port Harcourt and its environs PCa presents a serious health challenge. Its hospital incidence at the University of Port Harcourt teaching hospital (UPTH) is 114/100,000 [8].

Chronic inflammation is known to play a key role in human carcinogenesis including PCa [9]. Pro-inflammatory cytokines such as IL-6 and TNF-α play critical roles in the inflammatory processes that lead to tumour invasion and progression. Inflammation has been observed to precede cancer with emergent reports showing inflammation to be higher in men with high grade PCa [10]. Cytokines are water soluble, low molecular weight proteins or glycoproteins that transmit signals between cells [9,11].

Apart from serum-PSA, other preliminary tests such as histopathological investigations of PCa in needle biopsy specimens or post prostatectomy specimens may predict tumour behaviour that will help guide therapeutic interventions [9,12]. In clinical practice, pathological reports of PCa will include the grade of tissue differentiation according to Gleason's scores (GS) and the quantitative assessment of the tumour volume in each biopsy, either in length (mm) or in percentage (%) of a tumour. Histological patterns of malignant glandular architecture in haematoxylin-stained prostatic tissue determine the GS. The overall GS is obtained by adding up of pattern-numbers of the primary and secondary tissue grade ranging from 2-10 [13,14].

Gleason's scoring enables clinicians to quantify pathological aggressiveness of the disease and therefore is a key factor in determining treatment strategy in conjunction with the pre-treatment serum-PSA levels and TNM staging [14]. However, histological examination has its own demerits such as morphological mimics of prostate carcinoma for example adenosis (which is a non-cancerous condition), very low-grade carcinoma or atypical adenomatous hyperplasia which may interfere with accurate interpretation of tumour biopsy.

The present study evaluated serum concentrations of IL-6 and TNF-α before treatment and in metastatic PCa. The aim was to analyse the inflammatory patterns and the correlation between the pro-inflammatory IL-6 and TNF-α with GS (inflammatory pattern) before treatment.

2. Materials and methods

The subjects in this study were patients who presented at the Urology Clinics of the University of Port Teaching Hospital (UPTH), Nigeria for evaluation and treatment of prostatic diseases. Data was collected contemporaneously with evaluation, preliminary resuscitation in some cases, and confirmation of diagnosis of primary PCa.

This study employed the non-probability (quota sampling method) as subjects were chosen based on their satisfying a pre-specified criterion- histopathologically confirmed primary adenocarcinoma. Qualified subjects had histologically confirmed prostate adenocarcinoma with Gleason grading before treatment. Exclusion criteria included those on androgen deprivation therapy (ADT) or radiotherapy (RT). All patients enrolled in the study had their PCa classified as follows: well-differentiated (GS ≤ 6), moderately differentiated (GS = 7), and poorly differentiated (GS 8-10).

Approval of the present study was obtained from the Ethics Committee of UPTH, Port Harcourt, Nigeria. Written informed consent was obtained from all subjects for blood sample collection and prostate biopsy and histological grading prior to therapy from the Urology Division of the Surgery Department of UPTH.

Serum levels of IL-6 and TNF-α prior to treatment were measured. Serum IL-6 and TNF-α were quantified using capture enzyme-linked immunosorbent assay (ELISA) kits (Aviva System Biology, San Diego, CA, USA), serum- PSA (Monobind Inc 100 Norte Pointe Drive Forest, CA92630, USA). Assay kits were chromogen-based based and IL-6, TNF-α and serum-PSA concentrations were automatically determined by the reader using corresponding mean samples relative to the optical densities (ODs) on the standard curve. Quantities of reagents, the optimal temperature required, timing of reactions and end point of reactions were done in strict compliance with the ELISA kit manufacturer's instruction. The assays were done in the Chemical Pathology Research Laboratory at the University of Port Harcourt Teaching Hospital.

2.1. Statistical analysis

Statistical analysis was done with the statistical package for social sciences (SPSS) version 20.0 incorporated, Chicago IL USA. Frequency tables and charts were used to present categorical data. A test of significance was used to compare sample means. Descriptive statistics was done by calculating sample means and standard deviation. Finally, Pearson's product-moment correlation coefficient was conducted to measure the association between serum IL-6, serum TNF-α and the Gleason's score.

3. Results

A total of 90 patients between the ages of 52 and 83 years, who gave their consent were recruited for this prospective descriptive study. Inflammatory patterns in the malignancy were analysed and presented in tables. Table 1 shows the minimum and maximum levels of the inflammatory mediators in the serum of the patients. Tables 2 shows the frequency distribution of their ages.

Table 1 Minimum and maximum levels of 1L-6, TNF-α and serum PSA with standard deviation in prostate cancer subjects.

	N	Minimum	Maximum	Mean	Std. Deviation
IL6 pg/ml	90	2.80	70.90	8.0017	11.16842
TNF alpha pg/ml	90	11.20	172.03	27.0000	26.37404
GS	90	3.0	10.0	7.444	1.9552
Age	90	52.0	83.0	68.767	8.2613
PSA (ng/ml)	90	11.02	385.00	93.2421	78.00856

Table 2 Frequency distribution of subjects according to age groups.

	Frequency	Percent	Valid Percent	Cumulative Percent
<60	14	15.6	15.6	15.6
60-79	68	75.6	75.6	91.1
>80	8	8.9	8.9	100.0
Total	90	100.0	100.0	

Table 3 Frequency distribution of prostate cancer subjects in the Gleason score categories

	Frequency	Percent	Valid Percent	Cumulative Percent
Well Differentiated GS ≤ 6	17	17.8	17.8	100.0
Moderately differentiated GS = 7	27	31.1	31.1	31.1
Poorly differentiated GS 8-10	46	51.1	51.1	82.2
Total	90	100.0	100.0	

The tumours were classified according to their Gleason grades and levels of cellular differentiation (Table 3). Most tumours were poorly differentiated (Figure 1)

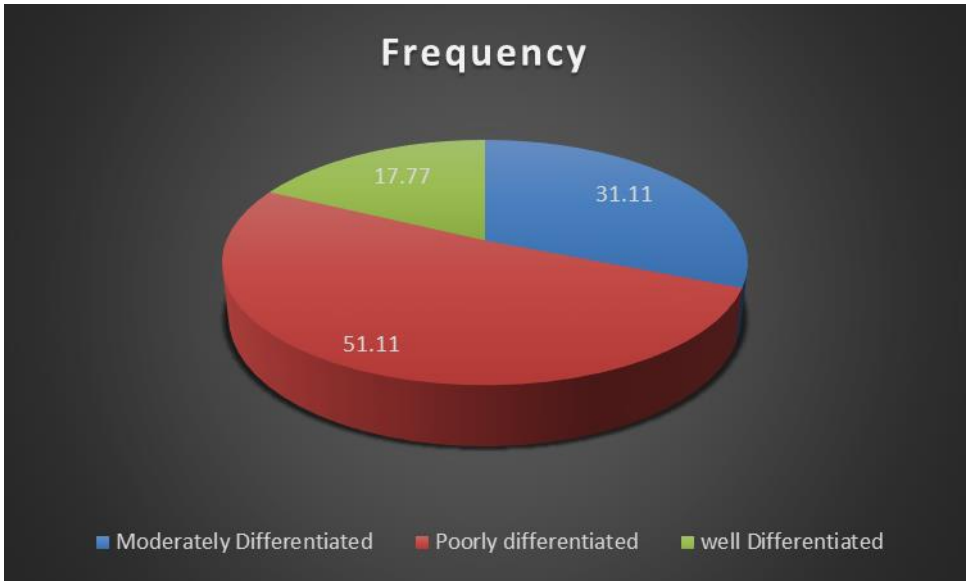

Figure 1 Distribution of prostate cancer subjects according to Gleason score

Table 4 The mean levels of IL-6, TNF-α and serum-PSA in the Gleason score categories

		N	Mean	Std. Error
IL6 pg/ml	Well Differentiated	27	5.26	0.21
	Moderately Differentiated	17	9.32	3.53
	Poorly Differentiated	46	9.12	1.89
	Total	90	8.00	1.18
TNF alpha pg/ml	well Differentiated	27	22.14	1.48
	Moderately Differentiated	17	21.63	2.03
	Poorly Differentiated	46	31.84	5.25
	Total	90	27.00	2.78
PSA (ng/ml)	well Differentiated	27	54.73	6.26
	Moderately Differentiated	17	100.78	19.49
	Poorly Differentiated	46	113.06	13.04
	Total	90	93.24	8.22

Table 5 Serum IL-6, TNF-α and serum PSA level between and with Gleasons score categories using ANOVA Test.

		Sum of Squares	df	Mean Square	F	Sig.
IL6 pg/ml	Between Groups	289.422	2	144.711	1.164	.317
	Within Groups	10811.860	87	124.274		
	Total	11101.282	89			
TNF alpha pg/ml	Between Groups	2203.674	2	1101.837	1.606	.207
	Within Groups	59703.828	87	686.251		

	Total	61907.502	89			
PSA (ng/ml)	Between Groups	59089.163	2	29544.581	5.327	.007
	Within Groups	482505.743	87	5546.043		
	Total	541594.905	89			

Table 6 Karl Pearson's Correlations between IL-6, TNF-α and serum PSA with Gleason score in prostate cancer subjects.

		IL6 pg/ml	**TNF alpha pg/ml**	**GS**	**Age**	**PSA (ng/ml)**
IL6 pg/ml	Pearson Correlation	1	-.024	.098	.006	.019
	Sig. (2-tailed)		.823	.357	.958	.861
	N	90	90	90	90	90
TNF alpha pg/ml	Pearson Correlation	-.024	1	.155	-.171	.535**
	Sig. (2-tailed)	.823		.143	.107	.000
	N	90	90	90	90	90
PSA (ng/ml)	Pearson Correlation	.019	.535**	.283**	-.116	1
	Sig. (2-tailed)	.861	.000	.007	.278	
	N	90	90	90	90	90

**. Correlation is significant at the 0.01 level (2-tailed).

	GS (Pearson Correlation)	
IL6 pg/ml	0.098	+ve Correlation (weak)
TNF alpha pg/ml	0.155	+ve Correlation (weak)
Age	0.052	+ve Correlation (weak)
PSA (ng/ml)	0..283	+ve Correlation (weak)

4. Discussion

The diagnosis of PCa still remains a great challenge even with the combination of several methods. Histopathologiacal analysis and GS are additional investigations required by clinicians to predict its outcome. Quite a number of clinical researchers have reported the significance of novel biomarkers that may be useful in the future as predictors of prognosis and development [16]. Several biomarkers, including cytokines, oncogenes, tumour suppressor genes (TSGs), cytokine receptors and hormone receptors are well established in clinical scientific literatures [17]. The role of pro-inflammatory cytokines such as IL-6 and TNF-α, in general cancer development including PCa has been established [9]. The main clinical challenge in PCa is the absence of ideal diagnostic tests, including the generally acknowledged serum-PSA screening and histopatholgical grading to differentiate between latent and aggressive tumours [18]. PSA is secreted by the epithelial cells of the prostate. Its normal reference level, although varies with age, in a normal prostate is 0-4ng/ml. Serum PSA concentration often increases in inflammation, prostatic hyperplasia and prostate adenocarcinoma [19, 20].

Conditions that may be associated with chronic inflammation of the prostate gland include urinary tract infection (UTI), poorly treated sexually transmitted diseases (gonorrhoea) [21]. bacterial (syphilis), [22] and viral (cytomegalovirus) [23] infections and prostatic trauma. Prostatic inflammation may eventually lead to proliferative inflammatory atrophy (PIA). PIA are lesions arising from the peripheral zone of the prostate as a result of inflammation. These lesions described as intermediate can progress to low-grade prostatic intraepithelial neoplasia (LPIN), high-grade postatic intraepithelial neoplasia (HGPIN) to prostatic neoplasia.

Gleason's histopathological grading of PCa is important as an indicator of prognosis and invasion in the tumour because it quantifies pathological aggressiveness [24]. GS of 8-10 represents a clinically aggressive form of the disease and is used to classify patients as high risk [25]. Therefore, in addition with the serum-PSA levels, age and TNM stage clinicians are guided on treatment decision-making.

In this study the serum-PSA levels, though highest in the (GS 8-10) category, the observed correlation is weakly positive (r= 0.283) and the observed difference was not statistically significant (p < 0.585).This present study showed that the serum levels of the cytokines (IL-6 and TNF-α) increased as the GS increased in the PCa patients. This compares with data obtained by Tazaki et al in 2011[26] in a research that profiled ten (10) serum cytokines in PCa patients whose result showed increases in IL-6 and TNF-α patients with confined PCa as compared to controls. The mean serum IL-6 and TNF-α levels slightly increased as the GS increased. It was lowest at GS ≤6 and highest at GS of 8-10. Milicevic et al [27] obtained similar results where serum levels of IL-6 was highest at GS>7 in PCa. Michalaki et al [28] also demonstrated serum levels of IL-6 significantly higher in patients with metastatic PC and GS > 6.

Data from this study showed increased levels of IL-6 and TNF-α at GS 8-10 but the correlation is weakly positive. P value for (IL-6) was r= 0.098, and that for TNF-α r =0.155. However, this observed increase in the GS grading 8-10 is not statistically significant as Pvalue for IL-6 was P = 0.545, and that for TNF-α 0.679. Higher levels of these cytokines are indication of the presence of chronic inflammation. The Gleason grading system may still remain the last resort and widely accepted prognostic factor for PCa as it plays a crucial role in predicting the progression of the disease even after a radical prostatectomy.

5. Conclusion

There was a weak positive correlation between IL-6 and GS (r =0.098) and between TNF-α and GS (r-0.155) respectively. This correlation may most likely be associated with the inflammation in the prostate. Further clinical studies, probably with larger sample sizes, may be necessary to validate these findings and identify biomarkers that can help predict patients' outcomes and improve therapeutic success.

Compliance with ethical standards

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Disclosure of conflict of interest

There is no conflict of interest.

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