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Negative Association of Chronic Inflammation with High-Grade Prostate Tumors Treated by Radical Prostatectomy

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Abstract

Background: Chronic inflammation of the uninvolved prostate has been identified as a potential contributor to the onset and progression of prostate cancer. The goals of this study were to identify the prevalence of chronic inflammation associated with high-grade prostate tumors and to investigate chronic inflammation's relationship with pathological stage and grade.

Materials and Methods: Consecutive series, retrospective chart review of pathologic data collected from 519 prostate tumors treated by radical prostatectomy. Histological evidence of chronic inflammation was assessed in prostate tissue specimens. Tumor differentiation and aggressiveness was quantified by final Gleason score and final pathologic stage (AJCC TNM staging system) assigned by surgical pathologist. Spearman's Rho non-parametric correlation was performed to measure the respective relationships of chronic inflammation with Gleason score and with pathologic stage.

Data/Results: Chronic inflammation of the uninvolved prostatic tissue was observed in 255 of the 519 prostatectomy specimens (48.6%). Chronic inflammation was inversely associated with final pathologic stage (T2-T4), corresponding with the following prevalence rate: T2a: 71.4%, T2c: 49.3%, T3a: 42.6%, T3b: 31.4%, T4: 0% (Spearman's rho = -.167, $p < .001$). Additionally, chronic inflammation was inversely associated with Gleason scores (GS6- GS10), corresponding with the following prevalence rates: GS6: 54.2%, GS7: 48.4%, GS8: 42.9%, GS9: 38.7, GS10: 0% (Spearman's rho = -.065, $p = .138$).

Conclusions: Chronic inflammation in the uninvolved prostate has been identified as a potential mediator of prostate cancer. The study data indicates that chronic inflammation was present in less than 50% of high-grade prostate cancers treated by prostatectomy. An inverse association between the prevalence of chronic inflammation and final pathologic stage was identified. A similar trend towards decreasing Gleason score in prostate cancers associated with chronic inflammation was noted. The study data indicates that poorly differentiated, highly aggressive prostate cancers are less likely to be associated with chronic inflammation.

Introduction

Recently published data from the American Cancer Society indicates that 233,000 estimated new cases of prostate cancer were diagnosed in 2014, with 29,480 estimated deaths from the disease [1]. Although several risk factors have been attributed to the development of prostate cancer, the pathogenesis of the disease is yet to be elucidated. Prostatic tissue uninvolved in the primary tumor may actively contribute to carcinogenic transformation. Recurrent or chronic inflammation in the uninvolved prostate has been identified as a potential contributor to prostate cancer tumorogenesis. Possible etiological factors in the genesis of chronic prostatic inflammation are an imbalanced diet, exposure to environmental pollutants, high circulating testosterone, bacterial and viral infection or genetic predisposition [2]. Inflammation, regardless of etiology, is thought to incite carcinogenesis by causing cell and genome damage, promoting cellular replacement and creating a tissue microenvironment rich in cytokines and growth factors that can enhance cell replication, angiogenesis and tissue repair [3]. Areas of chronic inflammation are commonly identified in radical prostatectomy specimens and prostate needle biopsies [4]. Gupta et al. analyzed the association between chronic inflammation and prostatic carcinoma in prostate biopsies specimens, showing that 20% of patients with chronic inflammation in initial biopsies were subsequently diagnosed with adenocarcinoma on follow-up biopsies during the next 5 years, suggesting a strong association between chronic prostatic inflammation and malignant changes [5]. Resnick et al. analyzed the prevalence of chronic inflammation in radical prostatectomy specimens, finding that chronic inflammation was associated with prostate cancer in 57.5 % of tissue specimens [6]. Multiple studies have examined the association between chronic inflammation and prostate cancer, but few existing studies correlate the prevalence of chronic inflammation to prostate tumor stage and grade. Karakiewicz et al. found chronic inflammation was more frequent in men diagnosed with low-grade

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prostate cancer, and chronic inflammation was inversely correlated with Gleason score in needle biopsy specimens [7]. The goal of this study was to identify the prevalence of chronic inflammation in high-grade prostate cancer specimens treated by radical prostatectomy and to determine its relationship with prostate tumor pathological stage and grade.

Methods

Patient population

Approval for this study was obtained from the University of Kentucky Institutional Review Board. Patients identified for inclusion into the study were adult males who underwent laparoscopic radical prostatectomy for treatment of prostate cancer performed by a single surgeon at the University of Kentucky Medical Center between 2003-2013. With application of inclusion criteria, 575 patients were considered for review, with 56 patients excluded for missing data, resulting in 519 patients included into the study. Study authors performed a consecutive series, retrospective chart review of patient charts and pathology reports obtained from prostatectomy specimens. Data extracted from patient charts included patient demographics and median pre-operative Prostate Specific Antigen (PSA).Data extracted from the pathology report included presence of high-grade prostatic intraepithelial neoplasia (HGPIN) and percentage of chronic inflammation associated with uninvolved prostate tissue, as well as Gleason Score and final pathologic stage for each identified prostate tumor. The reviewing surgical pathologist from the University of Kentucky Department of Pathology identified and documented HGPIN and percentage of chronic inflammation in the uninvolved prostatic tissue. The surgical pathologist assigned Gleason Score and final pathologic stage for each tumor identified in tissue specimen. Patients with T2 - T4 final pathological stage and Gleason score 6 – 10 were included into the study. Gleason score and final pathologic stage (AJCC TNM staging system) were used to quantify prostate tumor differentiation and aggressiveness.

Table 1: Patient Characteristics.

No. of patients	519
Median age in years, range (n=519)	61, 38-82
Median Preop. PSA, range (n=433)	5.7, 0.5 – 63
% High Grade PIN	81.3
% Chronic Inflammation	48.6
Gleason score n, %	
6	92, 17.7%
7	381, 73.4%
8	14, 2.7%
9	31, 6.0%
10	1, 0.2%
Final Pathologic Stage n, %	
T2a+b	42, 8.1%
T2c	369, 71.1%
T3a	68, 13.1%
T3b	35, 6.7%
T4	5, 1.0%

Statistical analysis

The relationships between the prevalence of chronic inflammation and HGPIN with pathologic stage and Gleason score were calculated using Spearman's Rho non-parametric correlation. Significance was set at $p < .05$. SPSS™ statistical software version 22 (IBM™ Corp., Armonk, NY) was used for all calculations.

Results

A total of 519 patients were identified for review after application of inclusion criteria. The clinical characteristics including age, median pre-operative PSA, percentage of patient with HGPIN, percentage of chronic inflammation in tissue specimens, number and percentage of patients with associated Gleason score and final pathologic stages are shown in (Table 1).

Chronic inflammation in uninvolved prostatic tissue was identified in 252 of 519 prostatectomy specimens. Preoperative PSA did not vary with the presence of HGPIN or chronic inflammation. PSA values did not vary by Gleason score or by pathologic tumor stage.The prevalence of HGPIN did not vary by Gleason score or by pathological tumor stage.

Chronic inflammation was inversely related to pathologic stage; ranging from 71% of stage T2a+b patients, 49% of T2c patients, 31% of stage T3b patients and none of the five T4 patients in the study. Stage T2c prostate cancers were highly represented in the study population, found in 369 patients (71.1%). Stages T3 through T4 prostate cancers were identified in 108 patients (20.8%). The statistical and percentage data for chronic inflammation associated with each pathologic stage included in the study is shown in Figure 1. (Spearman's rho = -.167, $p < .001$). Chronic inflammation was found to demonstrate a similar, but not significant inverse relationship with Gleason score (GS); ranging from 53% of GS 6 patients, 49% of GS 7 patients, 43% of GS 8 patients, and 38% of GS 9-10 patients in the study. Gleason 7 prostate tumors were highly represented in the study population, found in 381 patients (73.4%). Gleason grades 8-10 prostate tumors were identified in 46 patients (8.9%). The statistical and percentage data for chronic inflammation associated with each Gleason score included in the study is show in Figure 2.(Spearman's rho = -.065, $p = .138$).

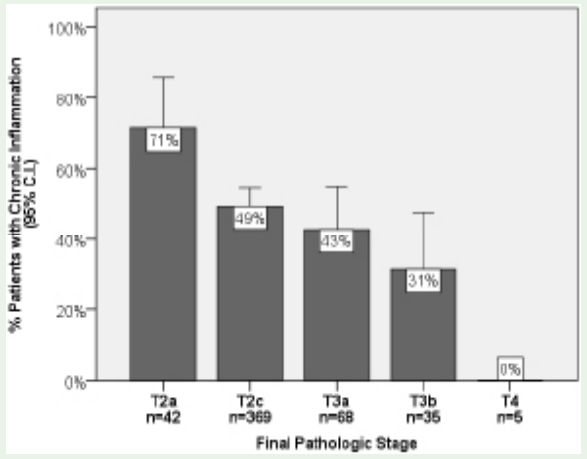

Figure 1: Negative Association of Chronic Inflammation with Pathologic Stage. Pathologic Stage was Inversely Related to Prevalence of Chronic Inflammation (Spearman's rho = -.167, $p < .001$).

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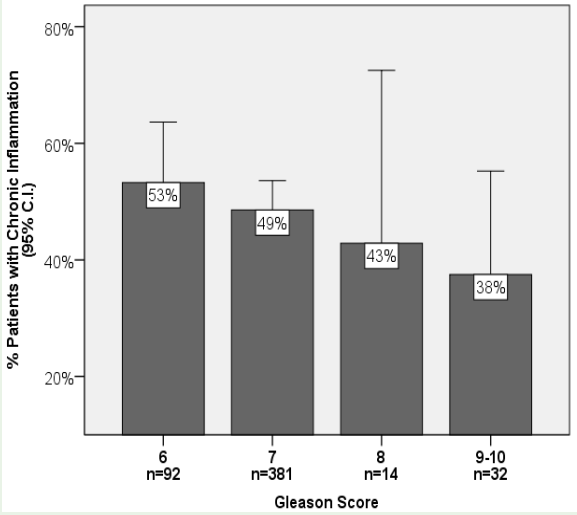

Figure 2: Negative Association of Chronic Inflammation with Gleason Score. Gleason score showed a similar trend but was not significant. (Spearman's rho = -.065, p=.138)

Discussion

The prevalence rate of chronic inflammation in prostate cancer tissue specimens was found to be 48.6%, indicating that chronic inflammation was present in less than 50% of prostate cancers treated by radical prostatectomy. Our study data indicate an inverse relationship between the prevalence of chronic inflammation and final pathologic stage in patients undergoing prostatectomy for treatment of high-grade prostate cancer. Additionally, there was a general trend towards decreasing Gleason score in prostate cancers associated with chronic inflammation. Final pathologic stage and Gleason score were the two primary means to evaluate the aggressiveness of prostate cancer in this study. The inverse association demonstrated by both pathologic stage and Gleason score suggests that poorly differentiated, highly aggressive prostate cancers, treated by radical prostatectomy, are less likely to be associated with chronic inflammation.

Our findings extend the findings of Karakiewicz et al. [7]., which showed that the presence of chronic inflammation was inversely related to the presence of prostate cancer in prostate tissue needle biopsy specimens. This study found that men with chronic inflammation were less likely to have prostrate cancer in needle biopsy tissue than less than men without inflammation. Additionally, this study demonstrated a similar inverse frequency of chronic inflammation according to increasing Gleason sum. Data demonstrating an inverse association between chronic inflammation in tissue and prostate cancer does not suggest causation.

The evidence to implicate chronic inflammation as a contributor in prostate cancer development remains in debate. It is hypothesized that, as for other cancers, chronic inflammation may increase the rate of mutations and damage to prostate cells and promote the proliferation of damaged cells, increasing the risk of prostate cancer [8]. Inflammatory cells contribute to increased vascularity, DNA damage, cytoskeleton remodeling and ECM degradation to provide a nurturing growth microenvironment for cancer cells [9]. It has been suggested that inflammation correlates with increased development of "risk factor" lesions or proliferative inflammatory atrophy (PIA). Chronic inflammation in benign prostate biopsy specimens has been associated with high-grade prostate tumors in adjacent areas. Gurel et al. reported that inflammation in benign prostate tissue was very common in both prostate cancer cases and controls, and the odds of total and high-grade prostate cancer increased with the extent of biopsy cores with inflammation [8].

While studies have suggested an associated between inflammation and an increased risk of prostate cancer development, our findings are consistent with opposing reports that do not support this hypothesis. Irani et al. demonstrated that inflammation was significantly lower in malignant prostatic tissue compared with the benign tissue [10]. Similarly, Gerstenbluth et al. reported that inflammation was more frequently associated with benign prostatic hyperplasia than cancer [6]. Furthermore, Zhang et al. identified that inflammation appeared to be more prevalent in prostate glands with lower grade tumors than in those with higher grade tumors [11].

Evidence has shown that the tumor microenvironment plays a crucial role in prostate cancer development and progression [12]. The microenvironment of poorly differentiated, highly aggressive tumors is vastly different than that of less aggressive tumors. Furthermore, the immune response against tumorcells is highly variable, as alterations of the tumor microenvironment which propagating aggressive cancer characteristics are not often recognized by the immune system [13]. Mutation in protooncogenes and tumor suppressor genes lead to profound changes for cells, including immortality, differentiation, an ability to invade and recruit new blood vessels, and the potential to metastasize to distant organs [14]. Cancer cells escape the immune system by masking or modulating cell antigens [7]. A heightened inflammatory response against prostatic tumor cells may confer a higher survival probability than tumors with a weak immune response. Findings by the study authors, and others demonstrating that inflammation is more likely associated with low-grade vs. high-grade malignant tissue supports the theory that highly aggressive prostate cancer may be antigenically different due to differences in the tumor microenvironment [6]. Poorly differentiated, highly-aggressive prostate cancer represented by increasing Gleason score and final pathologic stage may fail to provide the antigenic signals necessary to activate the inflammatory mechanism [6]. The ability to mount an immune reaction, which results in the presence of an inflammatory infiltrate, may represent the difference in the prevalence rates of inflammation seen according to Gleason score and pathologic stage [7].

While this proposed mechanism relating chronic inflammation to prostate cancer has been supported by this and other published studies, there remains limitations to establishing causation. Prostate cancer tissue reviewed in this study was obtained by radical prostatectomy. Data obtained from these tissue specimens is representative of men with definitively diagnosed prostatic disease with a level of aggression that warranted surgical removal vs. observation or other possible therapy modality. Therefore, the observations taken from this population are biased towards a more aggressive prostate cancer phenotype [7]. A population, which only includes aggressive disease, produces a limitation that does not allow for a comparative investigation of the prevalence of inflammation in benign prostatic tissue. Importantly, there is an inability to identify the role of inflammatory modulation of pre-neoplastic tissue during the progression to neoplastic, as researches are not able to obtain tissue

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from each stage of this continuum. It remains difficult to definitively elucidate the role of chronic inflammation in prostate cancer, but this data is a valuable contribution to the search.

Conclusion

Chronic inflammation has been identified as a potential contributor to tumorgenesis and progression of high-grade prostate cancer. This study data indicates that chronic inflammation was present in less than 50% of high-grade prostate cancers treated by prostatectomy. An inverse association between the prevalence of chronic inflammation and final pathologic stage was identified. A similar trend towards decreasing Gleason score in prostate cancers associated with chronic inflammation was noted. The study data indicates that poorly differentiated, highly aggressive prostate cancers are less likely to be associated with chronic inflammation. Chronic inflammatory responses to infectious agents, non-infectious inflammatory processes, and environmental factors may contribute to prostate cancer progression, but may not be responsible for promoting the aggressive nature of poorly differentiated, high-grade prostate cancer.

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