Original Article

Study of mast cells in prostate lesions: Adenocarcinoma compared with hyperplasia

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ABSTRACT

Background: (1) To study and correlate the mast cell numbers in benign prostatic hyperplasia (BPH) and prostate carcinoma lesions. (2) To compare mast cell numbers of intratumoral and peritumoral regions in prostate adenocarcinomas. (3) To ascertain a relationship between the number of mast cells and age, prostate-specific antigen (PSA) levels, and Gleason Grade. **Subjects and Methods:** One-hundred cases of prostate lesions, consisting of 75 cases of BPH and 25 cases of prostatic adenocarcinoma, received in the form of transurethral resection of prostate chips in the Department of Pathology, were included in the study. After histopathological diagnosis, the paraffin sections were stained with toluidine blue. **Results:** The mean value of mast cell count per mm^2 in benign and malignant lesion was 37.05 and 92.20, respectively. The difference in mean mast cell count in BPH and prostatic adenocarcinoma was found to be statistically significant ($P = 0.001$). The correlation between mast cell count and Gleason Grade was found to be statistically significant (*P*: Grades I–III - 0.043; 0.002; 0.012). However, no correlation was found between mast cell count with age and PSA levels. **Conclusion:** In this study, an increase in the number of mast cells was observed in patients with prostate cancer than in benign lesions. This suggests a stimulating role of mast cells in the progression of cancer.

Key words: Mast cell, prostate, toluidine blue

INTRODUCTION

Mast cells are connective tissue cells with basophilic metachromatic granules in its cytoplasm. Mast cells are usually found close to the blood vessels, nerves, sub-papillary dermis, superficial dermal plexus, and beneath epithelial surfaces.[1]

Mast cells play an important role in inflammation, hypersensitivity, and fibrotic disorders by producing and secreting various bioactive mediators.[2]

However, the role of mast cells in tumor is rather controversial. They can have a pro- or anti-tumor effect depending on the tumor type and tumor microenvironment.[3]

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Prostate cancer and benign prostatic hyperplasia (BPH) are the most common diseases affecting prostate and constitute over 90% of all prostate diseases. The infiltration by inflammatory cells in the prostate is considered one of the etiological factors in the development of BPH. Mast cells once triggered activate the fibroblasts and promote collagen synthesis by producing fibrogenic substances, thereby playing a role in chronic inflammation and fibrosis.[4]

Inflammatory cell infiltrates around the tumor generally act as a defense line against the tumor and may lead to better outcome in tumor affected patients. However, this finding is rather controversial as few studies have categorically stated that the mast cells play an important role in growth regulation of many tumors. One such tumor is prostate cancer and studies are underway to categorize the role of mast cells.

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Tissue markers with diagnostic and therapeutic value have been analyzed, but the prognosis of prostate diseases remains elusive. However, the role of mast cell as a promoter or suppressor of benign or malignant lesions of the prostate has not been ascertained in various studies. Based on these facts and controversies, we undertook this study to find the role of mast cells in benign and malignant lesions of the prostate.

SUBJECTS AND METHODS

One-hundred cases of prostate lesions were selected, which included 75 cases of BPH and 25 cases of prostatic adenocarcinomas.

The study was conducted in the Department of Pathology, Sri Devaraj Urs Medical College, Kolar, for 4 years. Specimens received in the form of transurethral resection of prostate chips, from Department of Urology, Shri RL Jalappa Hospital, attached to Sri Devaraj Urs Medical College and Research Centre, Kolar, were included. Patient details such as age, prostate-specific antigen (PSA) values were collected.

After histopathological diagnosis of the prostate lesions, the paraffin sections were stained with 1% toluidine blue for the examination of mast cells. On hematoxylin and eosin staining, mast cells resemble the fibroblasts, both in their shape (spindle or oval) and staining characteristics. Therefore, it is difficult to differentiate mast cells from fibroblasts on routine stains. One percent of toluidine blue helps in differentiating the mast cells. Mast cell granules were stained purplish-red and the nuclei stained sky blue [Figure 1].

Hotspots, with large number of mast cells, were identified for the counting [Figure 2]. Accordingly, they were counted in 10 high power fields (×40) with one field depth away from the basement membrane of the prostatic duct epithelium and the average number of mast cells per high field was determined. Mast cells were further expressed in per mm^2. Review of slides was done by two pathologists to eliminate the inter-observer bias.

Statistical analysis

Paired sample statistics was used to find difference in mean mast cell counts. The Pearson correlation was used to find correlation between mast cells and age, PSA levels. Wilcoxin signed rank test was used to correlate mast cells in adenocarcinoma and Gleason Grade.

RESULTS

The mean age of the patients with BPH was 50 years (ranged from 37 to 73 years), and prostatic adenocarcinoma was 63.64 years (ranged from 49 to 78 years). PSA levels in prostatic adenocarcinoma ranged from 12.25 to 104 ng/ml. Gleason score varied from 2 to 10. Serum PSA levels in BPH was within normal limits.

Table 1 presents quantitative data of mast cell infiltration for the patients with prostate cancer and BPH. In this study, it was found that mast cell numbers were significantly increased in prostatic carcinomas when compared to respective values in BPH.

The difference in mean mast cell count in BPH and prostatic adenocarcinoma was found to be statistically significant ($P = 0.001$).

Table 1: Quantitative data of mast cell infiltrates in prostatic carcinoma and benign prostatic hyperplasia

Lesions	Number of cases	Mean mast cell count (/mm^2)
BPH	75	37.05
Adenocarcinoma	25	92.20

BPH: Benign prostatic hyperplasia

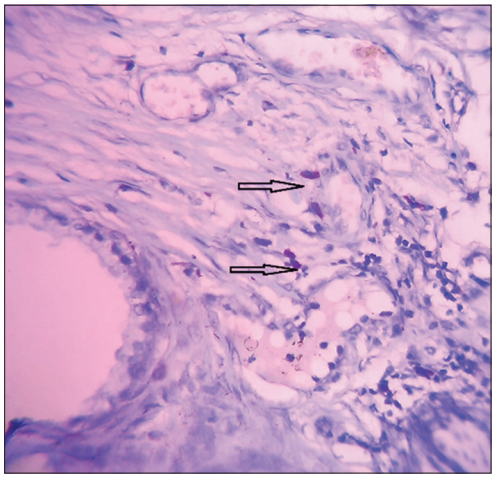

Figure 1: Mast cell infiltration around the prostatic gland in benign prostatic hyperplasia (×40)

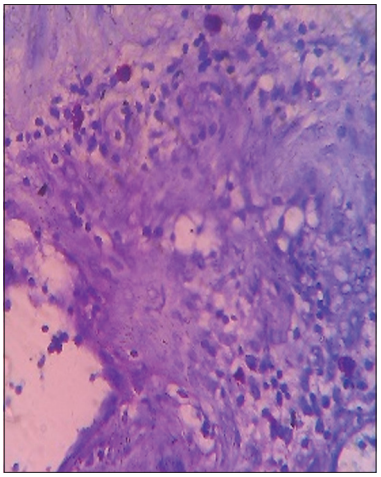

Figure 2: Area of "hotspot" showing mast cell infiltration in adenocarcinoma (×40)

We found mast cells to be concentrated along the blood vessel grouped in small cell clusters. Peritumoral mast cells were round or oval in shape, and intratumoral mast cells were elongated and often located in the glandular fold. The mean mast cell count in prostatic adenocarcinoma was 92.02. The mean mast cell count in the intratumoral region of adenocarcinoma was 9.64. The mean mast cell count in the peritumoral region of adenocarcinoma was 82.56. The difference in mean mast cells of intratumoral and peritumoral region was found to be statistically significant ($P = 0.001$).

There was no correlation between mean mast cell count and age of the patients with prostatic adenocarcinoma and was not statistically significant ($r = -1.22$; $P = 0.562$). The correlations between the number of mast cells and PSA levels were positive, but they did not reach statistical significance ($r = 0.432$; $P = 0.123$). Wilcoxin signed rank test was used to ascertain a correlation between the mast cell count and Gleason Grade, and it was found to be statistically significant (number of patients with Gleason Grade I - 8; Gleason Grade II - 12; Gleason Grade III - 5. (P: Grade I - 0.043, Grade II - 0.002; Grade III - 0.012) [Table 2].

DISCUSSION

In our study, we tried to find the role of mast cell infiltration in the prostate hyperplasia and prostate cancer and its associations with prognostic factors, such as Gleason score and serum PSA levels.

The presence of "mast cell" in tumor tissue was first reported by Ehrlich in the year 1878.[5] Mast cells are diverse in their functions. They play an important role in IgE-mediated disorders, act as immune-regulatory mediators, and take part in biological consequences such as mitogenesis, extracellular matrix degradation, and spread of tumors by recruiting various growth factors and cytokines.[6-9]

The tumor microenvironment consists of reactive stromal mixture of fibroblasts, endothelial cells, myofibroblasts, mast cells, and other immune cells. The mast cells being one of the stromal cells are attracted to tumor site by chemo-attractants such as stem cell factor (SCF), tumor-derived peptides, chemotactic activity elicited by RANTES or monocyte chemoattractant protein-1 and get activated and secrete molecules that act as growth factors aiding tumor growth, angiogenesis, and metastasis.[10]

Mast cells "remodel" the tumor microenvironment so as to promote tumor growth by increasing the secretion of inflammatory chemicals, thereby increasing the activity of nuclear factor-kappa B which increases the tumor's ability to suppress T-cell and natural killer cell attacks against it.[11] The growth and progression of adenocarcinoma depend on the activation of the stromal microenvironment.

In this study, we found significant increase in mast cell count in benign prostate hyperplasia with mean of 37.05, when compared to normal prostate mast cell count. Few studies have hypothesized the role of chronic inflammation, consisting of lymphocytes, plasma cells, macrophages, and mast cells as emerging factors in the development and progression of nodular hyperplasia.[12] Mast cells help in the progression of nodular hyperplasia by the release of their degranulated products and mediators. Our findings was supported by observations made by Stawerski *et al*. who also found mean of 72.82 cells/mm^2 mast cells in prostatic hyperplasia.[13]

The pro-tumor effects of mast cell is due to the secretion of histamine and growth factors such as vascular endothelial growth factors (VEGF), platelet-derived growth factor, SCF, nerve growth factor, and metalloproteases that contribute to the majority of proteolytic components necessary for tumor invasiveness.[14-16] The major pro-tumor effect of mast cell is the angiogenic activity brought about mainly by secreting VEGF, which is reflected by increased microvessel density in prostate cancer.[15-18]

The anti-tumor effect of mast cell is due to their degranulated products such as heparin which decreases the size and number of the tumor cells lying in proximity to the fibroblasts and tryptase which causes tumor cell disruption.

In our study, we found significant increase in number of mast cell count in prostate adenocarcinoma with mean count of 92.20 cells/mm. The infiltration was concentrated in the peritumoral region (mean count 82.56 cells/mm^2) than the intratumoral region (mean cell count 9.64 cells/mm^2) which supports the fact that there is increased activity and secretion of mast cell degranulated products at the peritumoral fronts which help in the progression of cancers. These findings were in agreement with the findings of Nonomura *et al*. (mean mast cell count was 16 cells/mm^2) and Globa *et al*. (mean 29 cells/mm^2) who also described increased mast cells in the peritumoral fronts of prostate cancers.[19,20] In a study done by Stawerski *et al*., they also

Table 2: Correlation between selected parameters and mast cell number in prostatic adenocarcinoma

Correlation	Age	PSA	Gleason grade
Adenocarcinoma	r=−1.22; P=0.562	r=0.432; P=0.123	Grade I - P=0.043 Grade II - P=0.002 Grade III - P=0.012

PSA: Prostate-specific antigen

found significant high number of mast cells in prostate adenocarcinomas (mean 123.73 ± 82.32 cells/mm^2).[13]

Johansson *et al*. observed a difference in the functionality of mast cells present in the intratumoral region from the peritumoural region. They stated that the mast cells, located within the tumor, inhibited angiogenesis, while peritumoural mast cells promoted it, stimulating tumor growth. Johansson's observations corresponded to the dual role of mast cell in tumorigenesis. His findings correlated with patients' clinical outcomes and treatment responses.[15] Similar observations were reported by Dyduch *et al*.[21]

We also correlated mast cell count with prognostic factors of prostate cancer such as Gleason score and PSA levels. The mast cell count and Gleason score correlations were statistical significance, (*P*: Grade I - 0.043, Grade II - 0.002; Grade III - 0.012) indicating higher the grade, higher the number of mast cell infiltration. They also showed positive correlations with PSA levels but did not reach statistical significance (P = 0.123). Similarly, Stawerski *et al*. observed significant positive correlations between the mean number of tryptase-positive cells and Gleason score, as well as between microvessel density and Gleason score. They also observed positive correlations between the number of mast cells and PSA levels and between microvessel densities and PSA levels, but they did not reach statistical significance. They concluded with the assumption that mast cell has a promoter function in prostate cancer development, and no evidence was found for their opposite.[13] This was in agreement with the findings observed in our study.

CONCLUSION

Our study observed a pro-tumor function of mast cells involved in formation and development of prostate cancer, thus suggesting that by targeting mast cells, it can aid in the prevention of nodular hyperplasia and prostatic adenocarcinoma progression. Anti-inflammatory agents have been tested *in vitro* and *in vivo* for the management of both conditions.[22,23]

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Conflicts of interest
There are no conflicts of interest.

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