Original Research Article

Consortum between mast cell and prostatic lesions-An etiological factor or mere coexistence

Vani D¹, Kumari Bhuvaneshwari S A^{1,*}, Bharathi M¹

¹Dept. of Pathology, Mysore Medical College and Research Institute, Mysore, Karnataka, India

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ABSTRACT

Introduction: Prostate cancer exhibits a complex genetic and heterogeneous histological pattern reflecting its multifactorial phenotype. Mast cells mainly known for their role in allergy and anaphylaxis, now regarded as key factor cell in angiogenesis, tissue remodeling and repair, whereas their importance in tumor pathology as either cancer promoter or inhibitor is still debated.

Materials and Methods: Study included 100 cases of prostatic lesions with 74 cases of benign prostatic lesions and 26 cases of adenocarcinoma prostate, received in the form of transurethral resection of prostate chips for histopathological examination. The tissues were routinely processed, the paraffin sections stained by hematoxylin and eosin and 1% toluidine blue. Histological diagnosis was made. Mast cell count was done taking a standard of 10 high power fields(x40) and mean were calculated. Distributions of mast cells were noted in stroma, perivascular, periglandular and intraglandular regions.

Results: Mast cell count was significantly higher in benign prostatic hyperplasia with mean of 3.6 per high power field whereas absence or low count was found in adenocarcinoma prostate with mean of 1.7 per high power field. Mast cells were located predominantly in stromal region in both BPH and adenocarcinoma prostate; in rest of the areas the numbers were comparable.

Conclusion: In this study we observed significant increase in mast cell count in stroma of BPH compared to adenocarcinoma indicating that mast cell density is inversely proportional to malignancy. This suggests high mast cell count favors the prognosis.

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1. Introduction

Prostate cancer is a multifactorial malignancy.¹ Despite milestone in intensive basic research on prostate cancer biology, mortality rate of prostate cancer still remains on higher side and is one of the leading cause of death worldwide in men.² American cancer society, estimates in its Cancer facts 2019 that there is probability of developing 174,650 new cases of prostate cancer and 31,620 deaths from prostate cancer.³ Manifestation of prostatic lesions range from indolent or asymptomatic to locally aggressive or metastatic.³

Tumors are commonly infiltrated by large number of immune cells which are scattered within tumor and loaded with array of cytokines, chemokines, inflammatory and cytotoxic mediators. This complex network reflects the assortment in tumor biology and tumor host interactions.¹ Indeed there are tale of evidence that suggest approximately 20% of all human cancers are attributable to chronic inflammation.⁴ Although inflammation plays a major role in development and progression of solid tumor, it still remains unclear whether inflammation caused aggressive disease or aggressive disease caused inflammation.¹

Several research groups proposed that in tumor inflammation, mast cells are found in most tumor types, which has progressively attracted the attention of basic and clinical researchers considering their ability to secrete a wide variety of effector molecule.⁵ Chronic inflammation

* Corresponding author.

E-mail address: bhuvialwandi93@gmail.com (K. Bhuvaneshwari S A).

in prostate is considered as one of the etiological factors in the development of BPH.⁶ It was Paul Ehrlich in 1878 first described accumulation of mast cells in tumor.¹ However mast cell interaction with tumor is related to microenvironment which largely determines the phenotype of the tumor.¹

Mast cells are granulocytic leucocytes originating from hematopoietic cells. Mast cells are pervasive and distributed throughout body especially in connective tissue, vessels and nerves that are closest to external surface.⁷ Mast cells known for their role in allergy and anaphylaxis now currently act as versatile, resourceful element in immune mediated angiogenesis, tissue repair, tissue remodeling and homeostasis.⁸

Mast cells in some tumors act as protumorigenic and influence the advancement of cancer cells by stimulating neovascularity. However this finding is rather controversial as few studies have stated that mast cells play an important role in hindering the tumor growth by its secretory proteins.⁹ In prostate cancer, no conclusive data on mast cell function are available and complex role of these cells remain poorly understood.

Overlooked in many studies the role of mast cells in prostatic tumorigenesis is discrepant finding which explains the heterogeneity and multifocality of prostate cancer in which several tumor foci with different molecular and proliferative characteristics may originate and coevolve within the same organ.¹ With prostate cancer being second most common cancer in males and incidence of castration resistant prostate carcinoma, high mast cell provide one such target. Considering all these facts we undertook this study to find out the role of mast cells in prostatic lesions.

2. Aims and objectives

1. To compare the mean mast cell count or densities in benign and malignant prostatic lesions.
2. To Study the distribution of mast cells in both benign and malignant prostatic lesions in stromal, perivascular, periglandular and intraglandular region.

3. Materials and Methods

Study included 100 cases of prostatic lesions with 74 cases of benign prostatic lesions and 26 cases of adenocarcinoma prostate, received in the form of transurethral resection of prostate chips for histopathological examination to department of pathology from June 2017 to march 2019. Patient details such as Age and PSA (Prostate specific antigen) values were collected.

The study was conducted in Department of pathology, Mysore Medical College and Research Institute. The tissues were routinely processed, the paraffin sections stained by hematoxylin and eosin and 1% toluidine blue. Histological diagnosis made by staining with hematoxylin and eosin.

On Hematoxylin and eosin staining mast cell resembles fibroblasts hence 1% toluidine blue helps to differentiate mast cells. Mast cell granules were stained purplish red and nuclei stained blue.

Mast cell count was done taking a standard of 10 high power fields(x40) and mean were calculated. Distributions of mast cells were noted in stroma, perivascular, periglandular and intraglandular regions.

3.1. Inclusion criteria

Benign prostatic hyperplasia and all grades of adenocarcinoma prostate and its variants.

3.2. Exclusion criteria

Inflammatory conditions like prostatitis, poorly preserved prostatic specimens, autopsy specimen and other malignancies of prostate like sarcoma s, transitional cell carcinoma were excluded.

3.3. Statistical analysis

All the data entered into Microsoft excel (windows 7; version 2007) and analyzed using SPSS software trial version 22.0.

4. Results

The study comprises of 100 cases of prostatic lesions out of which 74 cases were benign conditions and 26 of adenocarcinoma cases. Overall mean age of patient presented with benign prostatic hyperplasia was 55 years and prostate adenocarcinoma was 68 years. PSA levels in prostatic adenocarcinoma ranged from 24 to 98ng/ml.

Mast cell count was significantly higher in fibro muscular stroma in benign prostatic hyperplasia with mean of 3.6 per high power field Where as absence or low count was found in adenocarcinoma prostate with mean of 1.7 per high power field. The difference in mean mast cell count in benign and malignant condition was statistically significant with $P < 0.001$. We also found that mean mast cell number in other regions of periglandular, perivascular and intraglandular were comparable in both groups and found no significant difference.

The chi square test shows a significant difference in distribution of mast cells in stroma of BPH and Adenocarcinoma with P value being less than 0.001 as depicted in Table , Figure 1 and Figure 2

5. Discussion

In the present study we demonstrated the relation of mast cell count with benign and malignant condition, where we found that mast cell count in stroma was higher in benign hyperplastic hyperplasia compared to adenocarcinoma prostate.

Fig. 1: Photomicrograph showing stromal mast cells in BPH (40x Toluidine stain)

Fig. 2: Photomicrograph showing stromal mast cell in adenocarcinoma (40x Toluidine stain)

Amir et al¹⁰ and Gupta et al¹¹ findings of significant high mast cell count found in stroma compared to glandular area in BPH, with absent or low count in adenocarcinoma were in agreement with our study.

Bismay Das et al⁵ obtained similar results as our study where they observed maximum number of mast cells were concentrated in stromal region of BPH group compared to adenocarcinoma group and found no difference in the distribution of mast cell number in different regions.

In the study conducted by Jacob Schor⁹ et al after reviewing the published articles concluded that mast cell play a dual role and it appears to vary with cancer type. They drew inference that Mast cell appear to

promote the growth of cancer in following neoplasms : Rectal cancer, Melanoma, Squamous cell carcinoma of mouth and lips, NSCLC, Multiple myeloma, Hodgkin's lymphoma, Follicular lymphoma, Endometrial cancer, Pancreatic cancer, Thyroid cancer and Gastric cancer.

Here the pathological role of mast cell on tumor is linked to angiogenesis, related to release of inflammatory and proangiogenic factors like vascular endothelial growth factor and fibroblast growth factor.^{9,12} Also when the mast cells are stimulated in huge number they undergo degranulation and release large amount of preformed serine proteases such as tryptase and chymase, which stimulates proliferation of endothelial cells, promotes blood vessel proliferation and also degrades connective tissue matrix to provide space to angiogenesis.⁹

And the same study also explains the antitumorigenic role in which increased mast cell number correlated with improved prognosis in following conditions like Breast cancer, Ovarian cancer and Prostate cancer. Protumorigenic act of mast cell is explained here in context to heparin and histamine.⁹ The evidence includes localization of mast cells to fibrous region of tumors, the ability of heparin to inhibit tumor growth in vivo and in vitro in presence of fibroblasts and the accelerated growth of tumors in mice that were genetically or enzymatically depleted of heparin.⁹

In one of the study on tissue mast cells in breast cancer by Yang LP et al¹³ reviewed that exogenous histamine induces differentiation of immature myeloid cells and suppress their ability to support the growth of tumor allografts. Thus histamine increases myeloid cell differentiation and hinders early cancer development, supporting the hypothesis that triggering histamine might hinder cancer growth.

Yang LP et al¹⁴ in their study opined that histamine dihydrochloride along with cytokine interleukin enables the activation of T cells and NK cells by IL-2, resulting in killing of tumor cells of various cancers, including AML.

Agnes et al⁹ in their study on cancer patients, who suffered from thromboembolism and treated with heparin or coumorin, concluded that heparin had significant impact on survival.

These studies on both heparin and histamine in an attempt for clinical usefulness have not reached an agreement, which explains the varying effects mast cells have on cancer.

Decrease in the mast cell count in high grade adenocarcinoma prostate is explained in one of the study conducted by Paola Pittoni¹⁵ in which the study explains that poorly differentiated prostate tumors show epithelial mesenchymal transition which in turn produce matrix metalloproteinase 9 (MMP-9) autocrinously and are devoid of infiltrating mast cells both in mouse and in humans¹⁵ serving that mast cells exert different functions according to tumor stage. Mast cells favor initial tumor growth providing MMP-9 but become dispensable after epithelial

mesenchymal transition.

Johansson et al¹² found that in both non-malignant and malignant human prostate tissue, mast cells were found principally in stroma. In prostate tumors only a few mast cells were detected in the epithelial compartment. They also found that the mean number of mast cells in the nonmalignant stroma was significantly higher than in the tumor stroma similar to our study.

In contrast to our study Stawerski et al,¹⁶ Nonomura et al¹⁷ and Rakshith V et al⁷ drew inference of increased number of mast cells in patients of prostate cancer than in benign conditions suggesting a stimulating role of mast cells in progression of cancer.

Salivary gland tumors showed greater mast cell counts compared to normal salivary glands but benign neoplasms showed similar mast cell counts to malignant ones.¹⁸ Fakhrijou et al did not find a significant relationship between mast cell density and tumor differentiation.¹⁹

Aydin et al²⁰ investigated the utility of MCs in evaluating benign and malignant prostate lesions, and ascertained variations in the numbers of MCs with the Gleason grade. MCs were more frequently observed in the fibro muscular area than in the adenomatous area in BPH cases. There was a significant difference between mast cell density of intralesional and perilesional region with no statistical difference between Gleason score groups.

Mast cells have both beneficial and detrimental functions for host.¹ Given the current information on mast cells and cancer its challenging to study in which situations mast cells aid tumor growth and in which they suppress it and how we might utilize these studies for therapeutic advantage.

6. Conclusion

Our study observed significant increase in mast cell count in stroma of BPH compared to adenocarcinoma suggesting that mast cell count appears inversely proportional to malignancy, with no remarkable difference in distribution of mast cells in periglandular, perivascular and intraglandular region of benign and malignant prostatic lesions. This suggests that high mast cell count favors the prognosis in prostatic lesions.

Although this study was not designed to explore the molecular mechanism of how mast cells hinder tumor growth, therefore we propose that further molecular analysis of the interaction between mast cells and tumor is warranted for clarified insights.

7. Source of funding

None.

8. Conflict of interest

None.

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Author biography

Vani D Professor

Kumari Bhuvaneshwari S A Post Graduate

Bharathi M HOD and Professor

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