



## MAST CELL COUNT IN VARIOUS PROSTATIC LESIONS AND THEIR SIGNIFICANCE: A COMPARATIVE STUDY BETWEEN BENIGN PROSTATIC HYPERPLASIA AND CARCINOMA PROSTATE

### Histopathology

**Dr. Sanjeev Kumar** Junior resident, Pathology, Rajendra Institute of Medical Sciences, Ranchi

**Dr. Md. Alimuddin Ansari\*** Junior resident, Pathology, Rajendra Institute of Medical Sciences, Ranchi.  
\*Corresponding Author

**Dr. Sunil Kumar Mahto** Associate professor, Pathology, Rajendra Institute of Medical Sciences, Ranchi.

### ABSTRACT

In prostatic lesions, the role of mast cell infiltration varies with the type of the lesion. They mediate the biological consequences such as mitogenesis, extracellular matrix degradation and spread of tumors by recruiting various growth factors and cytokines. In BPH, there is significant increase in mast cell count when compared to normal prostate. Mast cells help in progression of nodular hyperplasia by release of their degranulation products and mediators. In Ca-Prostate, the pro-tumor effect of mast cells is due to secretion of histamine and growth factors such as VEGF, PDGF, SCF, Nerve growth factor and metalloprotease, that contribute to majority of proteolytic components necessary for tumor invasiveness. The major pro-tumor effect of mast cells is the angiogenic activity brought about mainly by secreting VEGF which is reflected by increased vascularity in prostate cancer.

### KEYWORDS

#### INTRODUCTION

Prostate gland is a functional channel that allows urine to pass from the urinary bladder to urethra and prostatic secretions add to semen during ejaculation.

Benign Prostatic Hyperplasia is a common benign disorder of prostate which represents nodular enlargement of the gland caused by hyperplasia of both glandular and stromal components resulting in varying degree of urinary obstruction.

Prostate cancer contributes significantly to overall cancer burden, being the most frequent neoplasia in men. The high life expectancy, western lifestyle and lack of physical exercise contribute to the rising incidence of prostate cancers.

Adenocarcinomas account for vast majority of all primary prostatic tumours. They are commonly multicentric and located at peripheral zones in 70% of cases. Prostatic adenocarcinoma is most commonly scored according to Gleason grading system, which is based on five histologic patterns of tumour gland formation and infiltration. Many prostate cancers are latent, asymptomatic, and undetected through standard diagnostic tests. There is a constant search for ancillary techniques to assist in the diagnosis.

Mast cell, first described by Paul Ehrlich in 1878, is a type of granulocyte derived from myeloid stem cells. It contains many granules rich in histamine and heparin, best known for their role in allergies and anaphylaxis. They also play important role in wound healing, angiogenesis, immune tolerance, defense against pathogens and maintenance of blood brain barrier. Mast cells are increased in correlation with enhanced tumor growth in Rectal cancer, Breast cancer, and Cutaneous malignancies.

Mast cells remodel the tumor environment to promote tumor growth by increasing the secretion of inflammatory chemicals, increasing the activity of nuclear factor kappa-B, which increases the tumor's ability to suppress T-cells and NK-cells attack against it.

#### MATERIALS AND METHODS

This study was conducted in the Department of Pathology with the help of Department of Surgery and, Department of Urology, Rajendra Institute of Medical Sciences (RIMS), Ranchi.

Cases comprised of patients admitted in the Department of Surgery and, Department of Urology, Rajendra Institute of Medical Sciences (RIMS), Ranchi.

The samples were obtained from the tissues received in the Department of Pathology for histopathological examination. The tissues comprised

of Core Biopsy of Prostate, Transurethral Resection of Prostate, and Total Prostatectomy (either Suprapubic or Transperineal approach) specimen. Total 75 cases were studied.

**TRUS needle biopsy:** The wide bore needle core (18G) specimens are counted and measured (in mm), submitted separately if labeled accordingly, painted with alcian blue for better visualization in paraffin block, and processed for initial histological examination.

**TURP chippings:** are weighed and sampled according to laboratory protocols.

For 12 gm or less of tissue, all is processed, for over 12 gm, 12 gm plus an extra 2 gm for every 5 gm of tissue in excess were processed. If carcinoma is found in any of the blocks, all tissue was processed. In case of previous diagnosis of carcinoma, only small amount of tissue (usually four cassettes) is sufficient.

**Radical prostatectomy specimens:** The specimen was oriented using the seminal vesicles (situated in posterior aspect) and by placing a probe in the prostatic urethra. This allows identification of base superiorly and the more conical apex inferiorly.

Entire specimen was weighed, prostate was measured in three dimensions along with length of attached seminal vesicle and vasa deferentia.

Right, left, anterior, posterior, superior and inferior surfaces of the prostate were painted using six different colored inks.

The specimen was fixed in 10% formalin for 24-36 hrs.

Seminal vesicle and vasa deferentia were dissected and sectioned serially.

Shaved sections of proximal and distal margins were taken.

After removal of the margins, serial sections were taken in coronal plane at 3-4 mm intervals from anterior to posterior. The slices were carefully examined maintaining the orientation with the help of colored inks.

Any tumor, if found, was described in terms of site (right/left, peripheral/central, anterior/posterior), size (in mm), appearance (soft/firm, pale/yellow/granular), edge (circumscribed/irregular), multifocality, extension beyond capsule/into seminal vesicles.

After proper dissection, each section was processed in tissue processor following standard processing protocols, followed by wax mounting

and section cutting on microtome. Two slides from each block was taken.

Following deparaffinization, one slide from each block was stained with Hematoxylin & Eosin, while the other slide was stained with Toluidine blue.

#### The H&E stain shows following structures:

- Nuclei - blue, black
- Cytoplasm - pink
- Muscle fibres - deep red
- RBCs - orange red
- Fibrin - deep pink.

Toluidine blue stains mast cells violet/red purple while the background appears blue.

Following proper mounting, each H&E stained slide was observed under microscope for their histological appearance and the number of mast cells count per mm<sup>2</sup> in respective toluidine blue stained slides.

#### 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.<sup>5</sup> 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.<sup>5</sup>

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.<sup>6</sup>

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.<sup>1</sup> 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/mm<sup>2</sup>, 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.<sup>4</sup> 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<sup>2</sup> mast cells in prostatic hyperplasia.<sup>3</sup>

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. 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.<sup>6</sup>

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<sup>2</sup>. The infiltration was concentrated in the peritumoral region (mean count 82.56 cells/mm<sup>2</sup>) than the intratumoral region (mean cell count 9.64 cells/mm<sup>2</sup>) 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<sup>2</sup>) and Globa et al. (mean 29 cells/mm<sup>2</sup>) who also described increased mast cells in the peritumoral fronts of prostate cancers. In a study done by Stawerski et al., they also found significant high number of mast cells in prostate adenocarcinomas (mean 123.73 ± 82.32 cells/mm<sup>2</sup>).

Johansson et al. observed a difference in the functionality of mast cells present in the intratumoral region from the peritumoral region. They stated that the mast cells, located within the tumor, inhibited angiogenesis, while peritumoral 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. Similar observations were reported by Dyduch et al. 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. This was in agreement with the findings observed in our study.

#### CONCLUSION

Mast cells are granulocytic immune cells best known for their role in allergy and anaphylaxis, with important functions in innate immunity against bacteria, viruses, and parasites. Since their first description in the late 19th century, mast cells were found aggregated around and within many types of solid cancers, but only in recent years the multiple functions operated by Mast cells in fostering angiogenesis, tissue remodeling, and immunomodulation in human and murine cancer have emerged.

Mast cells may exert pro- or antitumoral roles, depending on tumor type, on microenvironmental signals, and on neighboring interacting cells. It has been demonstrated that the infiltration of Mast cells at the tumor site can enhance tumorigenesis, although these findings are still debated.

Tumor-infiltrating Mast cells express multiple proinflammatory factors and increase IL-17 expression in tumor. Additionally, it is believed that Mast cells may impact upon the growth of tumors by multiple mechanisms, including angiogenesis.<sup>19</sup> Several studies have demonstrated that early angiogenic activity is dependent upon Mast cells and is an essential part of neoplastic development, with Mast cells mediating this activity by releasing heparin, VEGF, and IL-8.

The study of the role of Mast cells in prostate tumorigenesis is complicated by the multifocality of the prostate cancer, in which several tumor foci with different molecular and proliferative characteristics may appear and coevolve within the same organ. A fundamental question remains whether and how mast cells contribute to the development of immune privilege within the tumor microenvironment. It is now undubitable that a major point linking Mast cells to cancer is the capacity of these cells to synthesize and release potent angiogenic cytokines. It has also demonstrated that not only Mast cells stimulate tumor angiogenesis but also they promote lymphangiogenesis in different solid tumors. Ma et al. demonstrated that both tumor cells and pancreatic stromal cells (PSCs) stimulated Mast cell activation.

Conversely, Mast cell-derived interleukin- (IL-) 13 and tryptase stimulated PSCs proliferation. In prostate cancer, Mast cells have been recently indicated as novel independent prognostic markers, although previous studies on prostatic biopsies associated high MC densities with favorable tumor characteristics and good prognosis. An explanation for these appearing to be a discrepant finding remains the observation that prostate cancer is a multifocal and heterogeneous

disease. It has been ascertained that innate and adaptive immune cells commonly infiltrate solid tumors. Inflammation plays a major role in tumor progression. Overlooked in many studies of tumor inflammation, Mast cells are found in most tumor types.

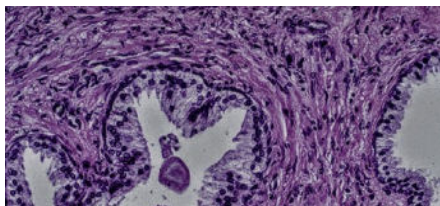
Considering their ability to secrete a wide variety of effector molecules, it is likely that Mast cells play an important role in many tumors, including prostate cancer. Some studies have shown that Mast cells are important proangiogenic effectors and inducers of the tumoral growth. Mast cells are, however, also known to be able to secrete a variety of molecules with antitumor effects. It has been suggested that the use of MC depletion/modulation therapies must be tailored toward each specific tumor.<sup>108</sup>

The term “biomarker” in oncological sciences refers to a large range of markers, including biochemical markers, cellular markers, cytokine markers, genetic markers, physiological results, radiological measurements, physical signs, and pathological assessment.

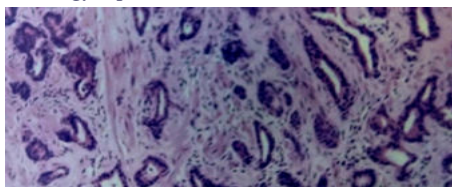
It has intuitive appeal to hypothesize that biomarkers with prognostic and/or predictive value are those intimately connected to the pathogenesis of human cancer. These include biomarker division into diagnostic (screening) biomarkers for early detection, prognostic biomarkers for estimation of disease outcome, predictive biomarkers for adjuvant treatment stratification, and surveillance biomarkers for monitoring progression disease and treatment response<sup>134</sup>.

Several proteins and genetic markers have been described in an attempt to refine prognostic information and predict the benefit derived from systemic treatment. The infiltrated host immune cell classification combined with some other biomarkers may have a prognostic value for tumor invasion and metastasis.

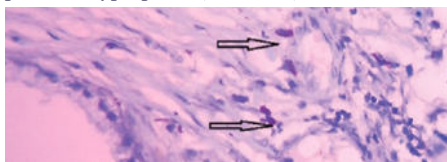
Further studies of MC function in different tumor types and subtypes should help us develop effective antitumor strategies utilizing manipulation of the number and function of mast cells



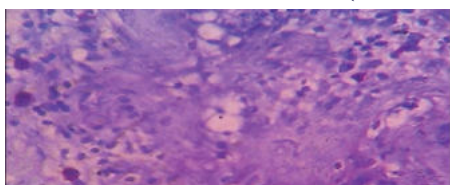
**Normal histology of prostate 40x H&E stain**



**Benign prostatic hyperplasia (H&E, 20x)**



**Periglandular infiltration of mast cells in BPH (toluidine blue, 40x)**



**Mast cell infiltration in adenocarcinoma prostate (toluidine blue, 40x)**

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