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Original Research Article

ROLE OF MAST CELLS IN UTEROCERVICAL PATHOLOGIES: A COMPARATIVE ANALYSIS OF BENIGN AND MALIGNANT LESIONS

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Abstract

Background: The cervix is susceptible to one or another pathologic condition-from inflammation to malignant disease-which is a fibromuscular structure with its squamous and columnar epithelium. Mast cell participation in immune responses has been included in tissue repair and angiogenesis. The density and functions of mast cells in these lesions are compared between benign and malignant lesions and influence tumor progression, prognosis, and eventual therapy. The aim and objective is to analyse and compare mast cell distribution and density in benign and malignant uterocervical lesions, evaluating their diagnostic, prognostic, and potential therapeutic significance. **Materials and Methods:** The present cross-sectional study was conducted in a hospital in Southern India for 12 months, which will analyse 90 hysterectomy specimens having uterocervical lesions. This study aims to assess mast cell density in uterocervical lesions using H&E and toluidine blue staining, analyzing specimens from 90 patients. Mast cell counts will be evaluated across benign, pre-malignant, and malignant lesions. Inclusion criteria include hysterectomy specimens from patients with uterocervical lesions, while exclusion criteria involve poor specimen quality, gestational uterus specimens, and autolysed tissue. Histopathological analysis will be performed on sections stained with H&E and toluidine blue to categorize lesions and evaluate mast cell density. **Result:** The study has shown that majority of patients (75.56%) were in the 30–35 year age group, with a smaller proportion (24.45%) in the 35–40 year range. Chronic cervicitis, the most common non-neoplastic lesion, had a mean mast cell count of 72.5, while other lesions had lower counts. Benign lesions, such as endocervical polyps and leiomyoma, showed significant differences in mast cell counts, with p-values of 0.001. **Conclusion:** The study indicates that chronic cervicitis is the most prevalent non-neoplastic uterine cervical lesion, with a higher mast cell count compared to other lesion types.

INTRODUCTION

The cervix is a fibromuscular structure that forms part of the uterus. It has a squamous and mucous-secreting columnar epithelium with a unique junctional area that is complete with basal cells. This area is prone to pathological alterations, from inflammation to malignancy. Cervical cancer is one of the most common cancers among women globally, with substantial regional variations in incidence. Congenital anomalies, benign lesions like leiomyomas, adenomyosis, endometrial polyps, and nabothian cysts, malignant tumors such as cervical and endometrial carcinoma, and endometriosis, polycystic ovaries, teratomas, benign and malignant ovarian epithelial tumors.[1,2]

The lesions of the uterocervical (UC) region can be classified into two: benign and malignant. Each of these has distinct characteristics. Benign lesions are non-cancerous and exhibit slow, localised growth, having well-defined borders and smooth surfaces, and therefore cannot spread to other parts.[3] Malignant lesions are cancerous, exhibiting a type of growth-fast and invasive; they have an irregular border and generally rough texture. Another difference is at the cellular level; the cells in benign lesions appear structurally organised and normal in histological appearance, while cells of malignant lesions have abnormal features such as irregular nuclei and higher mitosis. Malignant lesions, unlike the benign growths, can invade surrounding tissues and metastasize to distant sites in the body via the lymphatic and vascular systems.[3]

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Mast cells (MC) are considered important cells in the immune system which participate in inflammation, tissue remodeling, and also in the regulation of the immune responses. They release inflammatory mediators that regulate immune responses and promote vascular permeability.[4,5] MC work in a dual way; they mediate inflammation in terms of vasodilation or vasoconstriction, angiogenesis, and immune cell functions. MC also modulates innate and adaptive immune responses, which include the responses to all infectious agents and the usage of vaccine adjuvants. Their contributions to the primary immune responses will determine inflammation, fibrosis, and autoimmune diseases. MC are important in immune responses, inflammation, and tissue repair. Moreover, their functions are key in ensuring the balance and overall function of the immune system.[4-7]

MC have a significant role in the wound healing and angiogenesis in benign lesions; MC contributes to the process of tissue repair by secreting histamine and some angiogenic factors such as VEGF.[8] MC participates in the angiogenesis related to the tumor growth, wound repair, and tissue repair processes. Besides, MC are part of the angiogenic switch associated with hemangiomas, being involved in both proangiogenic and antiangiogenic functions at different stages.[8-10]

MC play a significant role in the tumor development process via their contributions to angiogenesis and immune evasion. They hold the potential to affect tumors through immunosuppression, angiogenesis, matrix degradation, and mitogenicity. MC are involved in the neoplastic development and advancement of different types of malignancies. These secrete pro-angiogenic agents, growth factors, and inflammatory mediators that can be of key influence on tumor growth and tumor metastasis.[11,12]

The density and functioning of MC varies between malignancy and benign lesions. There are about 2-3 times more tryptase-containing MC than chymase-containing MC at the periphery of the tumors malignantly formed concentrated at the edges of the tumor. Benign lesions do not show any differences in the number of MC that express tri-acylation or tri-amino acids.[13,14] MC play a crucial role in UC pathologies. They influence various aspects of diagnosis, prognosis, and potentially even treatment. They are useful in the differential diagnosis of certain conditions since the density and distribution are typically different between benign and malignant lesions. MC can participate in biological processes during the progression of tumors, through processes like angiogenesis, supporting the growth of the tumor, which can affect disease outcome. These cells are also pivotal in inflammation, vascular formation and tissue remodelling. This makes them targets for further therapeutic inhibition. Their activity could lead to an innovative treatment for the diseases such as recurrent pregnancy loss where MC hyperactivity promotes a diseased inflammatory environment.[15-17]

MATERIALS AND METHODS

Research Design: This cross-sectional study will be conducted on 90 patients, in the Department of Pathology in our hospital in Southern India, for 12 months. This study will examine hysterectomy specimens from uterocervical lesions to assess mast cell density using H&E and toluidine blue staining techniques. Mast cells will be counted in 10 consecutive high-power fields to identify variations across neoplastic and non-neoplastic lesions. Statistical methods will compare mast cell counts to evaluate their diagnostic and prognostic significance.

Inclusion and Exclusion Criteria

Inclusion Criteria

- This study will include 90 patients in the Histopathology Department for hysterectomy specimens and cervical biopsies.
- Hysterectomy specimens from patients with neoplastic and non-neoplastic uterocervical lesions.
- Specimens received in the pathology department during the one-year study period.

Exclusion criteria

- This study will exclude those participants with poor specimens, inadequately preserved tissue, and incomplete clinical details.
- Gestational uterus specimens.
- Autolysed hysterectomy specimens unsuitable for histopathological analysis.

Study Procedure

The selected 90 cases from the Department were analysed to evaluate the role of mast cells in uterocervical pathologies, which will compare their distribution and density in benign, pre-malignant, and malignant cervical lesions. The study will include 30 cases each of benign, pre-malignant, and malignant lesions. Specimens will be collected from hysterectomy procedures and cervical biopsies. All specimens will be fixed in 10% formalin for adequate fixation before processing to create paraffin blocks. Two sections will be obtained from the anterior and posterior surfaces of the cervix, with proper inking performed as required. Cervical biopsies will be embedded in toto. On the other hand, two serial sections will be prepared from each block. One section will be stained with Hematoxylin and Eosin (H&E), which follow histopathological findings under a light microscope at magnifications of 10X and 40X. The lesions will categorised into benign, pre-malignant, and malignant groups. The second section will be subject to 1% toluidine blue staining at a pH of 4.5 to determine and quantify mast cells. In addition, the stained sections are first analysed under low power (10X) to assess staining quality and then under high power (40X) to count mast cells. Mast cells are measured in 10

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consecutive high-power fields in each section, focusing on areas where the highest engagement of mast cells is observed. These fields' mean mast cell count is calculated to define mast cell density. Therefore, this analysis provides a comparative understanding of mast cell density and distribution across various uterocervical pathologies, highlighting their potential diagnostic and prognostic value.

Statistical Analysis: In order to conduct this study, we will use the analysis of variance (ANOVA) tool for this oneway t-test. In addition, the significant p-value can be taken as ≤0.05 as well as the R-software will be used for this analysis.

RESULTS

[Table 1] shows the distribution of patients by age group, with the majority falling in the 30–35 year range, comprising 75.56% of the total cases (68 out of 90 patients). The remaining 24.45% of patients (22 cases) were in the 35–40 year age group. This distribution highlights a predominant concentration of cases in the younger age bracket.

In [Table 2], the variation of mast cells in non-neoplastic uterine cervical lesions is presented. The most common lesion type, chronic cervicitis, accounted for 65.56% of cases (59 patients) and had a mean mast cell count of 72.5 per 10 high-power fields (HPF), with a standard deviation of 28.21. The range of mast cells in this group varied from 21 to 124 per 10 HPF. Other lesion types such as endocervicitis, microglandular hyperplasia, and endometriosis had lower mean mast cell counts, with means of 54, 36.5, and 22.58, respectively. The p-value for chronic cervicitis was 0.211, suggesting that the variation in mast cell counts across these non-neoplastic lesions is not statistically significant.

[Table 3] focuses on neoplastic uterine cervical lesions. Among benign lesions, the endocervical polyp group, which consisted of 6 cases (6.67%), had a mean mast cell count of 58 per 10 HPF, with a range from 20 to 96. The leiomyoma group (2 cases or 2.23%) had a mean of 52 per 10 HPF, with a range from 36 to 68. Both of these benign lesion types showed significant differences in mast cell counts, with p-values of 0.001. A benign mesenchymal tumor had a single case with a mean mast cell count of 48, but the statistical analysis could not be performed due to the lack of variability. The premalignant lesion, Low-Grade Squamous Intraepithelial Lesion (LSIL), had 3 cases (3.34%) with a mean count of 32.5 per 10 HPF, and this also showed a significant difference with a p-value of 0.001. These results suggest that mast cell counts are significantly higher in certain benign and premalignant lesions compared to non-neoplastic lesions.

[Table 4] shows the mean Mast Cell Counts in Non-Neoplastic and Neoplastic Lesions of the Cervix and compares the findings of various studies related to mast cell counts in several lesions of the cervix. The mean mast cell count in our 2023-2024 study for chronic cervicitis, a non-neoplastic lesion, was 72.5, which differs significantly from other studies, such as Gousuddin et al. (2015), 70.6 and Naik et al. (2004) with 103.8. Endocervicitis had the lowest in our survey with 54, which implies minimal mast cell involvement; this differs from other studies with higher mast cell counts, for instance, 63 in Gousuddin et al. (2015). Non-existent mast cell counts in cervical dysplasia and carcinoma were witnessed in our study and found to correlate with the findings of Mainali N and Sinha AK (2014), who had also recorded meagre figures for these lesions.

Table 1: Age-wise patients distribution.

Age Group (in years)	No. of Cases	Percentage (%)
30–35	68	75.56%
35-40	22	24.45%
Total	90	100%

Table 2: Variation of mast cells in non-neoplastic uterine cervical lesions

Lesion Type	No. of Cases N = 71	Range (/10 HPF)	Mean	SD	SE	P-value
Chronic Cervicitis	59 (65.56%)	21–124	72.5	28.21	1.65	0.211
Endocervicitis	3 (3.34%)	26–82	54	13.98	6.99	
Microglandular Hyperplasia	2 (2.23%)	14–59	36.5	20.28	9.07	
Endometriosis	7 (7.78%)	0	22.58	12.28	4.31	
Total	71 (78.89%)					

Table 3: Variation of mast cell in neoplastic uterine cervical lesion

Category	Lesion Type	No. of Cases	Range (/10 hPF)	Mean (/10 hPF)	SD	SE	p-Value
Benign	Endocervical polyp	6 (6.67%)	20–96	58	33.66	9.71	0.001
	Leiomyoma	2 (2.23%)	36–68	52	16.7	5.91	0.001
	Benign mesenchymal tumour	1 (1.12%)	48	48	0	0	0
Premalignant (n=30)	LSIL	3 (3.34%)	16–49	32.5	13.11	4.6	0.001
	HSIL	1 (1.12%)	10–41	25.5	23.53	8.32	0.001
Malignant (n=30)	Squamous cell carcinoma	3 (3.34%)	8–17	10.5	7.68	2.42	0.001
	Adenocarcinoma	2 (2.23%)	3–32	17.5	20.5	14.5	0.001

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	Small cell carcinoma	1 (1.12%)	16	16	0	0	0
Total		19 (21.12%)					

Table 4: Comparison of mean mast cell counts in non-neoplastic and neoplastic lesions of the cervix.

Study	Chronic Cervicitis	Endocervicitis	Cervical Dysplasia	Cervical Carcinoma
Gousuddin M et al. (2015)	70.6	63	42	16.5
Naik R et al. (2004)	103.8	102.57	0	48.08
Kalyani R and Rajeshwari G (2015)	48.38	66.96	41.95	34.6
Mainali N and Sinha AK (2014)	81.9	114.00	6.75	13.50
Our study from 2023 to 2024	72.5	54	36.5	22.58

DISCUSSION

MC in uterine and cervical tissues contribute to diverse physiological and pathological processes, being directly involved in several tissue repair mechanisms, through angiogenesis and the degradation of collagen. MC plays a crucial role in ensuring proper implantation and maintaining immune tolerance by influencing immune responses. They also show the ability to inhibit smooth muscle cell proliferation. In tumor biology, MC are known for their influence on tumor growth dynamics and vascular development. They also allow the extracellular matrix remodeling through their secreted proteases tryptase and chymase for structural tissue alteration.[18,19]

Jain et al. (1977) studied the MC distribution and stromal changes in 100 benign and 100 malignant uterine cervical lesions. MC were found to be mostly located near cervical glands or adjacent to proliferating fibroblasts. The comparative Mast Cell Density (MCD) evaluation demonstrated an increase in MCD to be associated with inflammatory processes of benign conditions, while marked reduction or complete absence was evident in malignant lesions. MC were found to be inversely associated with the levels of anaplasia and mitotic activity in malignant lesions, proposing a possible connection between tumor aggressiveness and MC depletion.[20]

Naik et al. (2004) studied the MC distribution in 50 neoplastic and 50 non-neoplastic uterine cervical conditions. They reported that the mean count of MC decreased to 44.8 in chronic cervicitis with ulceration, whereas the highest mean count of 250 was seen in cervical polyps. The MC counts were also increased in papillary endocervicitis (102.57) and chronic cervicitis (103.8). Under non-neoplastic conditions, MC were mainly positioned adjacent to cervical glands and blood vessels. In carcinoma of the cervix, MC count varied with an average count of 48.08. Significant invasion was found to correlate with reduced MC counts compared with a minimum invasion. MC distributed around tumor deposits. MCDs were compared. MC were observed to be increased in chronic inflammatory processes, while MC numbers were reduced or totally absent in neoplastic conditions. Inverse relationships between MC numbers and both the extent of anaplasia and the frequency of mitotic figures were established.[21]

Cabanillas-Saez et al. (2002) studied the presence of MC in normal and neoplastic tissues of the human uterine cervix. Tryptase-positive (MCT) and tryptase/chymase-positive (MCTC) MC were found to be present in both normal and neoplastic samples. The MCT phenotype was mainly expressed in normal tissues and benign and malignant cervical lesions. Given the angiogenic potential of tryptase, these findings indicated that in advanced malignancy, increased levels of MCT in cervical tissues led to the creation of a highly vascularized microenvironment that supported tumor proliferation and spread.[22]

MC modulation in benign lesions will ease symptoms from MC activation. In malignant uterine-cervical lesions, MC-targeted therapies will benefit from the use of angiogenesis inhibitors or anti-inflammatory agents. MC involved in inflammation and angiogenesis likely have a role in tumor progression; therefore, MC are good candidate therapeutic targets. Studies show MC variations in benign and malignant lesions. These differences possibly correlate to treating strategies in relation to various uterine-cervical conditions. Further investigations based on MC modulation will provide new avenues of therapeutic approach for benign and malignant lesions of the UC region.[20-23]

There are limitations in our current understanding of MC roles in UC pathologies. Evidence reveals that MC contributes to cervical remodeling in parturition, whereas ovarian steroids have been mentioned to exert an influence on MC. For cervical pathologies, Mast Cell Density vary; increased counts in nonmalignant conditions have been viewed as indicating inflammation and reduced or absent counts in cancers. MC counts vary greatly in various neoplasms of the cervix. There is need for further investigations in order to fully clarify the complex roles of MC concerning UC pathologies.[20,21,24]

Further investigation may open novel therapeutic targets if cervical cancer's molecular network was deeper understood and studied involving pathways like the RAF/MEK/ERK, PI3K/AKT, and the Wnt/b-catenin pathway. For better and safer fertility treatment, researching on the molecular mechanisms guiding decidualization in endometrium should be on the forefront. Furthermore, investigating the role of the NLRP3 inflammasome in cervical ripening may open up new avenues for therapeutic management of preterm labor and other complications of delivery. Understanding the genetic contribution to cervical insufficiency and the

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role of connective tissue in its pathogenesis may lead to better clinical management strategies.[25-27]

CONCLUSION

The study indicates that chronic cervicitis is the most prevalent non-neoplastic uterine cervical lesion, with a higher mast cell count compared to other lesion types. Benign lesions, such as endocervical polyps and leiomyoma, show significant variation in mast cell counts, suggesting a potential association between mast cell presence and lesion type. These findings highlight the importance of mast cells in cervical lesion pathology. The present study demonstrated a progressively decreasing mean mast cell distribution and density from the non-neoplastic to neoplastic lesions compared to each other. It was also noted that there was an inverse relationship between mean mast cell density and grade of dysplasia, potentially providing a useful prognostic marker.

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