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ORIGINAL RESEARCH

Significance of mast cells in non-neoplastic and neoplastic lesions of uterine cervix

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Abstract— Background: Mast cells are involved in multiple biological events. The significance of mast cells in non-neoplastic and neoplastic lesions of the cervix has been studied with conflicting results. Its presence in a tumor has been described as evidence of host immunologic antitumor response, angiogenesis and tumor invasion. **Aims/Objectives:** To study mast cell density in various cervical lesions using Toluidine blue stain. To compare the sections studied with conventional Toluidine blue staining and Toluidine blue staining by reducing the pH. **Methodology:** Cervical biopsy/hysterectomy specimens from archives of the Department of Pathology were considered for the study. The sections were studied for histomorphology and mast cell density. The mast cell density was assessed by Toluidine blue staining by conventional method and another method by reducing pH using weak HCL. The stained slides were reviewed for mast cell density under 10 high power field and statistically analyzed. **Results:** Total of 100 cases was studied. Normal cervix 7 cases with the mean age of 44.29 and the mean mast cell density of 45.43. Chronic cervicitis and polypoidal endocervicitis were 26 and 28 cases, the mean age of 45.38 years and 39.14 years and the mean mast cell count of 48.38 and 66.96 respectively. Intraepithelial lesions and malignancy were 23 and 16 cases, the mean age of 43.56 years and 52.26 years and the mean mast cell of 34.47and 34.6 respectively. The maximum number of mast cells was seen in polypoidal endocervicitis and the least number in squamous cell carcinoma of cervix. **Conclusion:** The role of mast cell differs in inflammatory and neoplastic lesions of cervix. Mast cells has an active role in inflammatory lesions.

Key words: Cervix, cervicitis, cervical intraepithelial neoplasia, cervical cancer, Toluidine blue

INTRODUCTION

Mast cells were first described by Paul Ehrlich in 1878 as the effect, particularly in the early and acute phases of allergic reactions. It has been only in the past two decades that mast cells have gained recognition for their involvement in other physiological and pathological processes (Mainali et al., 2014). Mast cells are heterogeneous group of immune cells involved in multiple biological events. They are a component of cancer microenvironment, the role of which is complex and poorly understood. The significance of mast cells in non-neoplastic and neoplastic lesions of cervix has been studied with conflicting results (Gousuddin et al., 2015).

The presence of mast cells in tumor has been described as evidence of host immunologic antitumor response and if they are abundant the prognosis is good. However, according to other studies, granules of mast cells are involved in angiogenesis and tumor invasion. Mast cells promote cancer growth by stimulation of neoangiogenesis, tissue remodelling and by modulation of the host immune response (Dyduch et al., 2012).

In this study, we tried to demonstrate and compare the presence of mast cell in various neoplastic and non-neoplastic conditions as well as their value as a prognostic indicator with the relationship of mast cell number.

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MATERIALS AND METHODS

The study was undertaken in the Department of Pathology at MVJ Medical College Hosakote, Bangalore over a two-year period from June 2013 to June 2015. All the cervical biopsies and hysterectomy specimens received were considered for the study. Relevant clinical information regarding age, parity, clinical features and provisional diagnosis were obtained from the hospital records. The blocks and slides were retrieved from department archives. Hematoxylin and Eosin [H&E] stained slides were reviewed and lesions were categorized as non-neoplastic and neoplastic lesions. Cases with incomplete clinical details and non-availability of blocks / slides were excluded from the study.

Non-neoplastic lesions were 61 cases consisting of 7 cases of normal cervix, 26 cases of chronic cervicitis and 28 cases polypoidal endocervicitis. Neoplastic lesions were 39 cases consisting of 16 cases of low grade squamous intraepithelial lesions (LSIL), 6 cases of high grade squamous intraepithelial lesions (HSIL), 1 cases of low grade cervical glandular Intraepithelial Lesion (CGIN), 16 cases of Squamous cell carcinoma (SCC). LSIL included Koilocytic change and Cervical Intraepithelial neoplasia-1 (CIN-1). HSIL included CIN-II and CIN-III (Darragh et al., 2012). CGIN showed tufting of endocervical lining epithelial cells with increased N:C ratio and without nuclear atypia.

The blocks were selected; 3-4μm thin sections were cut and stained with Toluidine blue to identify the mast cells with the typical metachromatic granules. Initially 1% Toluidine blue stain was used. Later 1% Toluidine blue stain of pH 4.5 was used which showed better visualization of mast cells.

The stained slide is first seen under low power to assess the quality of the stain. Mast cells were counted under 40X magnification for 10 consecutive fields in each slide in areas where maximum mast cells were seen and mast cell density (MCD) was calculated. Mast cell density of different histomorphological group were compared and analyzed by Analysis of Variance (ANOVA) statistical method. The sections of conventional Toluidine blue staining and Toluidine blue staining by reducing the pH are also compared.

RESULTS

Total of 100 cases were included in this study which comprised of 61 cases of non-neoplastic lesions (Normal cervix - 7, chronic cervicitis - 26 and polypoidal endocervicitis - 28cases) and 39 cases of neoplastic lesions (LSIL-16, HSIL-6, CGIN-1, SCC-16 cases). The age distribution in various non-neoplastic and neoplastic lesions is shown in **Table 1**. Age distribution and mast cell count of various non-neoplastic and neoplastic lesions are shown in **Table 2** and **3** respectively.

P value of <0.05 was considered significant. The age distribution in non-neoplastic lesions were not statistically significant (P value 0.087), however it was significant in neoplastic lesions (P value 0.02) as the age difference between LSIL/HSIL to cervical cancer was 10 years. Mast cell counts in non-neoplastic lesions were statistically significant (P value 0.008), as mast cells were maximum in polypoidal endocervicitis. In neoplastic lesions it was not statistically significant (P value 0.349). However, the count was low in SCC compared to LSIL and HSIL.

DISCUSSION

Mast cells are developed in the bone marrow and mature under local tissue microenvironment in the tissues. Mast cells are normally present around the blood vessels, skin, gastrointestinal tract and lungs, sites where it is exposed to foreign /external agents. Mast cells act as a first defense against invasion by outside agents (Theoharides and Cochrane, 2004).

Role of mast cells in inflammation

Mast cells play an important role in various allergic and inflammatory conditions. Mast cells have membrane bound granules that contain a variety of biologically active mediators like histamine, proteoglycans, leukotriene (LT C4, D4, and B4), prostaglandin D2 and Platelet activating factor (PAF). These mediators cause vasodilatation, increased vascular permeability, smooth muscle spasm and cellular infiltration with inflammatory cells (Dyduch et al., 2012).

Role of mast cells in neoplasia

Mast cells also play an important role in tumor progression, the role of which is complex and poorly understood. Mast cells promote cancer growth by modulation of cancer microenvironment which includes

fibroblasts, myofibroblasts, newly formed blood vessels and inflammatory cells. Mast cells act in cancer microenvironment as both promoter and inhibitor of tumor growth (Dyduch et al., 2012).

Table 1. Age distribution in various cervical lesions

Age Group(yrs.)	Normal cervix	Chronic cervicitis	Polypoidal endo-cervicitis	LSIL	HSIL	CGIN	Carcinoma	Total no. of cases
20-29	01	01	04	01				07
30-39	02	05	09	03	02		2	23
40-49	**02**	**11**	**11**	**09**	**02**	**01**	**5**	**41**
50-59	02	03	03	03	01		5	17
60-69		04	01		01		4	10
70-79		02						02
Total no. of cases	07	26	28	16	06	01	16	100

Table 2. Comparison of age distribution and mast cell count in various non-neoplastic cervical lesions

	Non- neoplastic Lesion	No. of cases 61	Range	Mean	Standard Deviation	Standard error of mean	P value	Remarks
Age (Years)	Normal Cervix	07	35 -56	44.29	7.27	2.74	0.087	**Not significant**
	Chronic cervicitis	26	28-75	45.38	12.36	2.42		
	Polypoidal Endo-cervicitis	28	21-60	39.14	8.9	1.69		
Mast cell count/10hpf	Normal Cervix	07	21-79	45.43	20.04	7.57	0.008	**Significant**
	Chronic cervicitis	26	11-95	48.38	20.00	3.92		
	Polypoidal Endo-cervicitis	28	15-107	**66.96**	26.28	4.96		

Table 3. Comparison of age distribution and mast cell count in various cervical neoplastic lesions

	Neoplastic Lesion	No. of cases 39	Range	Mean	Standard Deviation	Standard error mean	P value	Remarks
Age (years)	LSIL	16	24-56	42.56	7.79	1.94	**0.02**	**Significant**
	HSIL	6	32-60	44.60	10.78	4.402		
	CGIN	01	44	-				
	SCC	16	35-68	**52.26**	10.68	2.27		
Mast cell count/10hpf	LSIL	16	10-93	44.06	27.49	6.87	**0.349**	**Not significant**
	HSIL	6	20-70	41.66	16.17	6.60		
	CGIN	01	10	10				
	SCC	16	2-79	34.6	28.78	7.19		

Table 4. Relation between Age range and mean mast cell count

Age Range(Yrs)	Range of Mast cell count /10hpf	Average of Mast cell count /10hpf
20-29	10-95	55.0
30-39	3-107	50.7
40-49	10-96	54.0
50-59	10-79	42.2
60-69	2-67	38.9
70-79	20-30	25.0

Table 5. Shows that as age advances the average mast cell count decreased

Normal Cervix		
Serial No.	**Age**	**Mast cell count/10hpf**
1.	35	55
2.	38	44
3.	40	79
4.	45	52
5.	46	22
6.	50	45
7.	56	21

Table 6. Shows mean age in non-neoplastic and neoplastic lesions of cervix in various studies

Mean age in Years					
	Normal cervix	**Chronic Cervicitis**	**Polypoidal endo-cervicitis**	**Cervical dysplasia**	**Carcinoma cervix**
Mainali N et al (2014)	40.11	45.67	37.28	-	49.50
Gousuddin et al (2015)	-	39.6	36.4	39.8	49.6
Present study-(2015)	44.29	45.38	39.14	43.15	52.26

Table 7. Shows the mast cells in non-neoplastic and neoplastic lesions of cervix

Mean Mast Cell Count					
	Normal cervix	Chronic Cervicitis	Polypoidal endo-cervicitis	Cervical dysplasia	Carcinoma cervix
Naik. R et al (2004)	-	103.8	102.57	-	48.08
Mainali N et al(2014)	80.56	81.90	114.00	6.75	13.50
Gousuddin et al(2015)	-	70.6	63	42	16.5
Present study	45.43	48.38	66.96	41.95	34.6

Mast cells as tumor promoters

Mast cells release proangiogenic and mitogenic factors and are involved in the degradation of the extracellular matrix. Histamine released by mast cells induces tumor proliferation through H1 receptors and suppress the immune system through H2 receptors and Interleukin-10 (IL-10), and tumor necrosis α (TNF-α). Mast cells also release proangiogenic factors such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), transforming growth factor-β (TGF-β), IL-8 and matrix metalloproteinases which are involved in extracellular matrix degradation. Mast cells release chemical mediators that cause vasodilatation, edema with protein rich exudate. Perhaps such a milieu favours tumor invasion and spread.

Mast cells in inhibition of tumor growth

The antineoplastic actions include direct inhibition of cell growth, increased inflammatory activity, induction of apoptosis and decreased cell mobility. Mediators released by the mast cells i.e. TNF-α, IL-1 and IL-6 have inhibitory effect on tumor growth and angiogenesis (Dyduch et al., 2012).

In the present study mast cells were mainly present in the areas of inflammation, sub-epithelial stroma and around dilated endocervical glands. In the present study, age distribution was not statistically significant in non-neoplastic lesions; however, it was significant in neoplastic lesions. The observation of our study showed that the age in cervical cancer was 10 years more than that of cervical intraepithelial lesions. These findings were similar to other studies in the past as shown in **Table 6**. The results of the present study are correlating with other studies. A ten-year interval is very well evident between cervical dysplasia and carcinoma.

A study done by Mainali et al showed that mean mast cell count was more in polypoidal endocervicitis which was similar to the present study as shown in **Table 7**. The mast cell count was significant in non-neoplastic lesions. Majeed SK studied distribution of mast cells in various organs of mice and showed that there is increased number of mast cells in the inflammatory lesions. Jain PC et al showed an increase of mast cells in inflammatory processes (Majeed, 1994). In our study also there is a well-established relationship in non-neoplastic lesions of uterine cervix with the mast cell count being more in polypoidal endocervicitis (**Table 7**).

The statistical study showed no correlation with reference to mast cells in neoplastic lesions. However, among the neoplastic lesions least mast cell count was seen in SCC (**Table 3**).

Table 7 shows the mast cell count in non-neoplastic and neoplastic lesions of cervix. Some studies have shown maximum in chronic cervicitis compared to polypoidal endocervicitis. However, in other studies maximum count was seen in polypoidal endocervicitis compared to chronic cervicitis as in our study (Mainali et al). Comparing the mast cell count between non-neoplastic and neoplastic lesions in various studies it was observed that the count was decreased in neoplastic lesions of cervix as in our study. Comparing the mast cell count in cervical dysplasia and carcinoma cervix, some studies showed increase in mast cell count in carcinoma cervix compared to cervical dysplasia, in other studies the count is more in cervical dysplasia compared to carcinoma cervix as in the present study (Gousuddin et al., 2015). Mean mast cell count was more in non-neoplastic lesions and least in SCC of cervix.

However, in one of study they showed that there is no correlation between the mast cells and age of the patient (**Table 4)**. There is inverse relation between mast cell count and degree of dysplasia(Sridharan and Shankar, 2012) and probably related to decrease in immunity with advancing age (**Table 5**).

The observation of progressively decreasing mast cell counts from mild to severe dysplasia and invasive carcinomas, suggests that mast cell count appears inversely proportional to the degree of dysplasia.

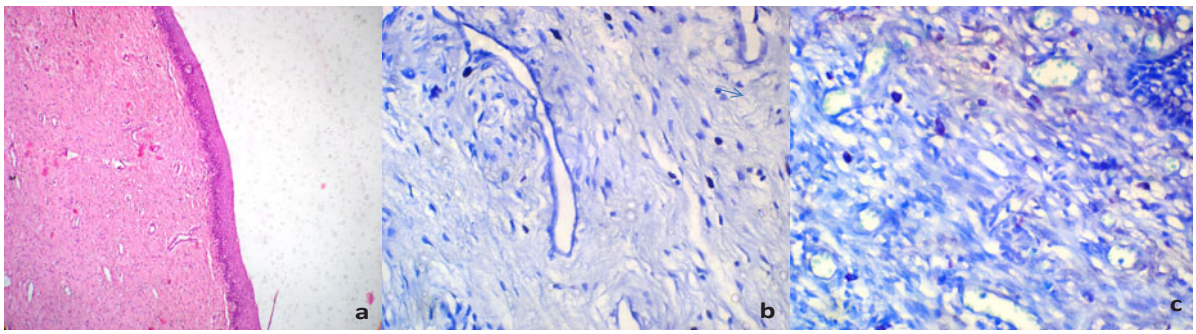

Figure 1. Chronic cervicitis. a.H & E (x100), b. Toluidine blue (x400), c. Toluidine blue pH 4.5 (x400).

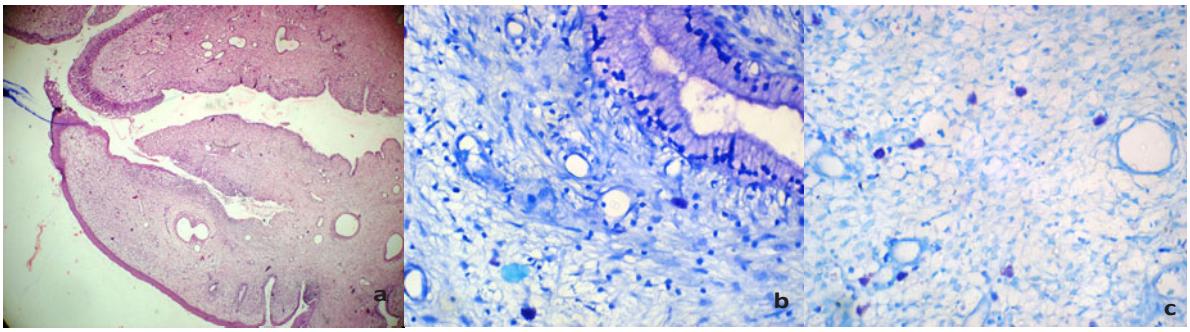

Figure 2. Polypoidal endocervicitis. a.H & E (x100), b. Toluidine blue (x400), c. Toluidine blue pH 4.5 (x400).

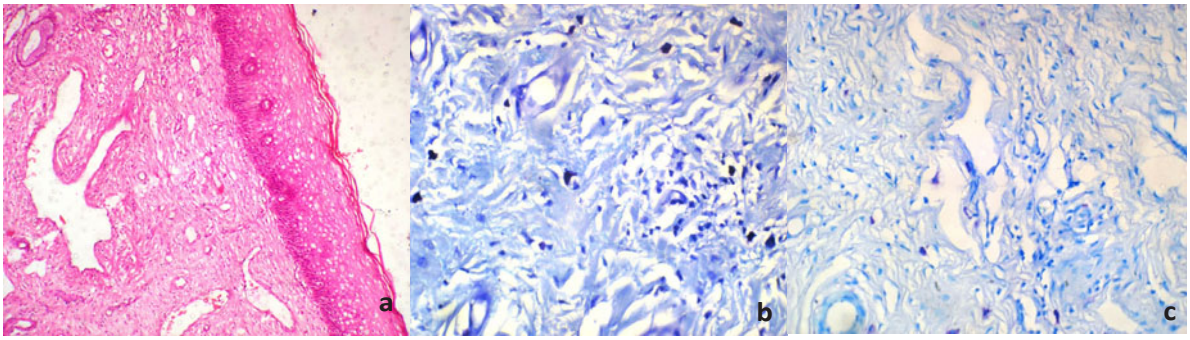

Figure 3. LSIL. a. H & E (x100), b. Toluidine blue (x400), c. Toluidine blue pH 4.5 (x400).

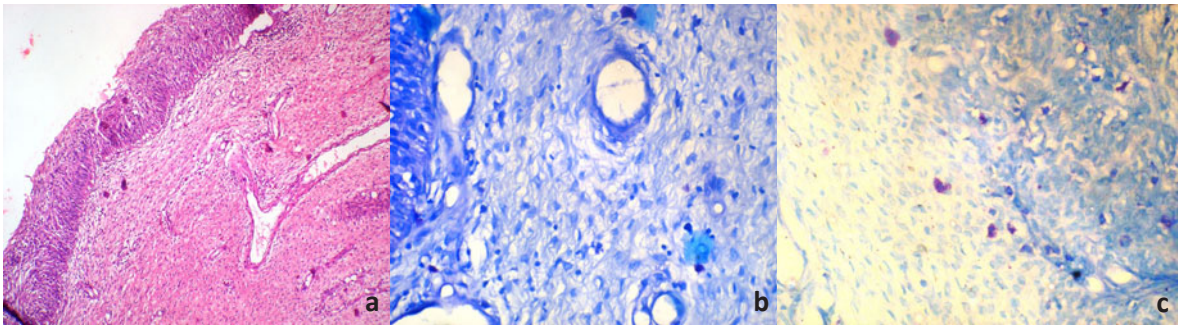

Figure 4. HSIL. a. H & E (x100), b. Toluidine blue (x400), c. Toluidine blue pH 4.5 (x400).

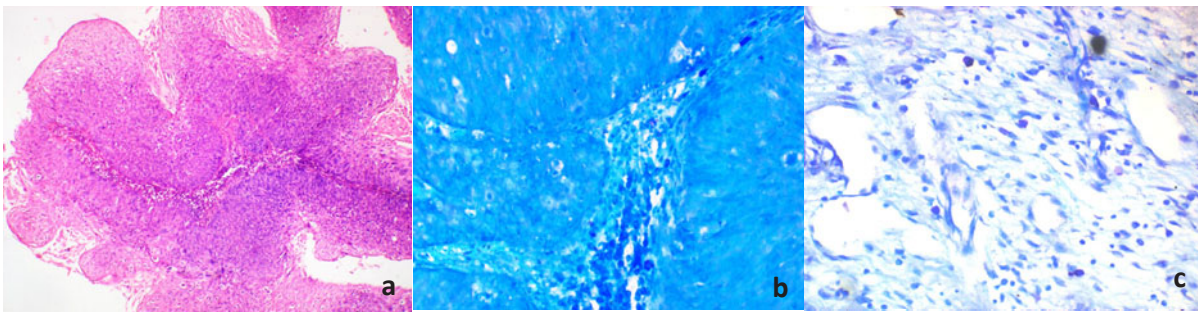

Figure 5. SCC. a. H & E (x100), b. Toluidine blue (x400), c. Toluidine blue pH 4.5 (x400).

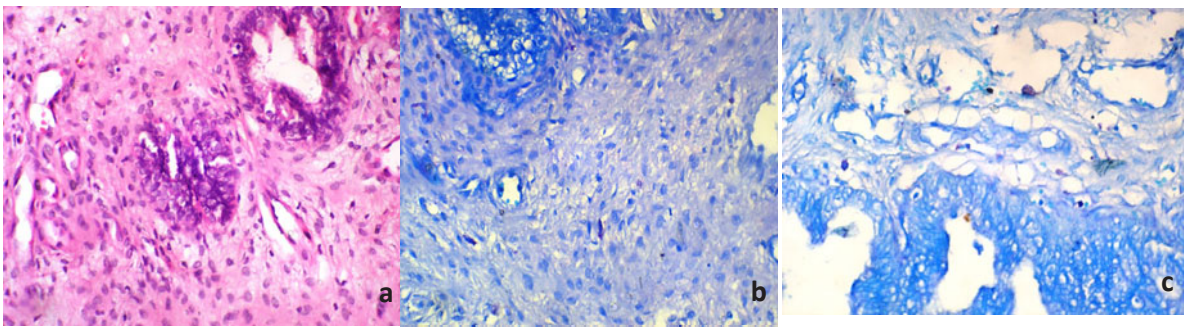

Figure 6. CGIN.a. H & E (x100), b. Toluidine blue (x400), c. Toluidine blue pH 4.5 (x400).

CONCLUSION

Mast cells are increased in inflammatory lesions of cervix with maximum in polypoidal endocervicitis and least in SCC of cervix. There is statistical significant correlation with reference to mast cells in non – neoplastic lesions and it was not statistically significant with reference to age. In neoplastic lesions statistical significant correlation was observed with reference to age but it no statistical correlation was observed with reference to mast cells.The role of mast cell differs in inflammatory and neoplastic lesions of cervix; indicating active role in inflammatory lesions.

Competing interests

The authors declare that they have no competing interests.

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