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A Study on Evaluation of Mast Cells in Papulo-Squamous Lesions of Skin

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Abstract

Context: Papulosquamous lesions are a broad variety of dermatological disorders that encompass non infectious papular and squamous lesions known to have a varied distribution of mast cells. The role of mast cells in the pathogenesis of skin lesions like lichen planus is evident by the increase in their number and morphological alterations of these cells as noted by few authors. *Aims:* To quantify and evaluate mast cells in various papulosquamous diseases. *Methods and Material:* A total of 50 cases of papulosquamous skin lesions were retrieved from archives. H & E sections were reevaluated to confirm the diagnosis. Sections from representative blocks were cut to stain with Toluidine blue. They were evaluated for mean number of mast cells by evaluating three 40X high power fields. The mast cells were assessed for mean mast cell number, location, granularity and morphology. *Results:* Among 50 cases selected 3 were rejected due to insufficient block material. 17 cases of lichen planus(LP), 10 cases of psoriasis vulgaris (PV), 6 cases of discoid lupus erythematosus (DLE), 2 each of pityriasis lichenoid rosaeca, lichen plana pilaris, lichen simplex chronicus and 1 each of 8 other miscellaneous lesions. Mean mast cell number for LP, PV and DLE were 7.5, 8.7 and 5.8 respectively. Degranulation and spindled morphology was observed in 88%, 50% and 100% in LP, PV and DLE. *Conclusions:* The mast cells present in the lesions can bear influence on the pathogenesis of papulosquamous lesions by release of mediators to induce histological alteration characteristic of these lesions.

Keywords: Mast Cells; Papulo-Squamous Lesions; Skin.

Introduction

Mast cells were first described by Paul Ehlrich in 1878. He named them Mastzellen (fattened or well fed cell) as he suspected their granules contained phagocytosed material [1-4]. Holmgren and Willander observed the high content of heparin in tissues rich with mast cells in 1937. The discovery of histamine release from mast cells during anaphylactic shock was made in 1952 by Riley and West. Since then, the mast cells have been traditionally regarded as effecter cells of allergy. When a multivalent antigen cross links IgE bound to IgE receptors on mast cell surface, aggregation of receptors promotes the release of mast cell mediators. These enzymes and cytokines mediate the classic features of allergy such as increased vascular permeability, mucus secretion, smooth muscle contraction etc [1,2].

In the recent times they have been attributed to other physiological processes such as tissue repair, wound healing and angiogenesis. Their crucial role in innate and acquired immune responses has been accepted [1,5].

The focus of research in the last decade has been to establish and study the role of mast cells in disease processes apart from the well known allergic reactions. We discuss the attributes and implication of mast cell presence in few dermatologic conditions we encountered.

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Materials and Methods

A retrospective cohort study of 50 cases was

conducted from the period of January 2012 to May 2014. Inclusion criteria included various papulosquamous skin lesions diagnosed using Hematoxylin and eosin stain. H & E sections were reevaluated to confirm the diagnosis. Sections from representative blocks were cut to stain with Toluidine blue. Three high power fields (400X magnification) were assessed in order to standardize the amount of tissue evaluated in each case [6]. The cases were recorded for mean mast cell number per standardized field, granularity (Degranulated / granulated), location (perivascular/random/ both) and morphology (rounded / spindled). Perivascular, periadenexal and areas of cellular infiltrate were selected for counting mast cells. Mast cells were categorized as granulated or degranulated, round or oval/spindle shaped. Intact granulated mast cells exhibit intense cytoplasmic metachromasia obscuring nucleus, degranulated mast cells show less intense metachromasia and clear outline of nucleus [4].

Results

Among 50 cases selected, three were rejected due to insufficient block material. The cases included 17 cases of lichen planus(LP), ten cases of psoriasis vulgaris (PV), six cases of discoid lupus erythematosus (DLE), two each of pityriasis lichenoid rosaeca, lichen plana pilaris, lichen simplex chronicus and one each of eight other miscellaneous lesions (Figure 1). Mean mast cell number for LP, PV and DLE were 7.5, 8.7 and 5.8 respectively (Table 1). However Lichen macular amyloidosis was showing the highest mean mast cell number of 15 and the lowest of three by keratopilaris and pityriasis lichenoids. Mast cells were located predominantly in the perivascular region in PV and evenly distributed in cases of LP and DLE. Degranulation and spindled morphology was observed in 88%, 50% and 100% of LP, PV and DLE (Table 2).

Table 1: Distribution and location of mast cells in papulosqaumous lesions

Papulosquamous lesion	No. of cases	Mean mast cell number	Location of Mast cell		
			Perivasular	Random	Both
Lichen Planus	17	7.5	7	2	8
Poriasis vulgaris	10	8.7	8	0	2
DLE	6	5.8	2	0	4
Pityriasis Lichenoid Rosacea	2	11.5	1	0	1
Lichen plana pilaris	2	11	0	0	2
Lichen simplex chronicus	2	11.5	1	0	1
PRP	1	8	1	0	0
Keratosis pilaris	1	3	1	0	0
Confluent retentional papillomatosis	1	11	1	0	0
Lichen psoriasis	1	5	1	0	0
Lichen macular amyloidosis	1	15	1	0	0
Lichen planus pigmentosus	1	6	1	0	0
Erythema dyschrmomium perstans lichen	1	6	1	0	0
Pityriasis Lichenoides	1	3	1	0	0

Table 2: Morphology and granulation of mast cells in papulosqaumous lesions

Papulosquamous lesion	No. of cases	Morphology		Granulation status	
		Rounded	Spindled	Granulated	Degranulated
Lichen Planus	17	2	15	2	15
Poriasis vulgaris	10	5	5	5	5
DLE	6	0	6	6	0
Pityriasis Lichenoid Rosacea	2	2	0	2	0
Lichen plana pilaris	2	1	1	1	1
Lichen simplex chronicus	2	1	1	1	1
PRP	1	0	1	0	1
Keratosis pilaris	1	0	1	0	1
Confluent retentional papillomatosis	1	0	1	0	1
Lichen psoriasis	1	0	1	0	1
Lichen macular amyloidosis	1	1	0	1	0
Lichen planus pigmentosus	1	0	1	0	1
Erythema dyschrmomium perstans lichen	1	1	0	1	0
Pityriasis Lichenoides	1	1	0	1	0

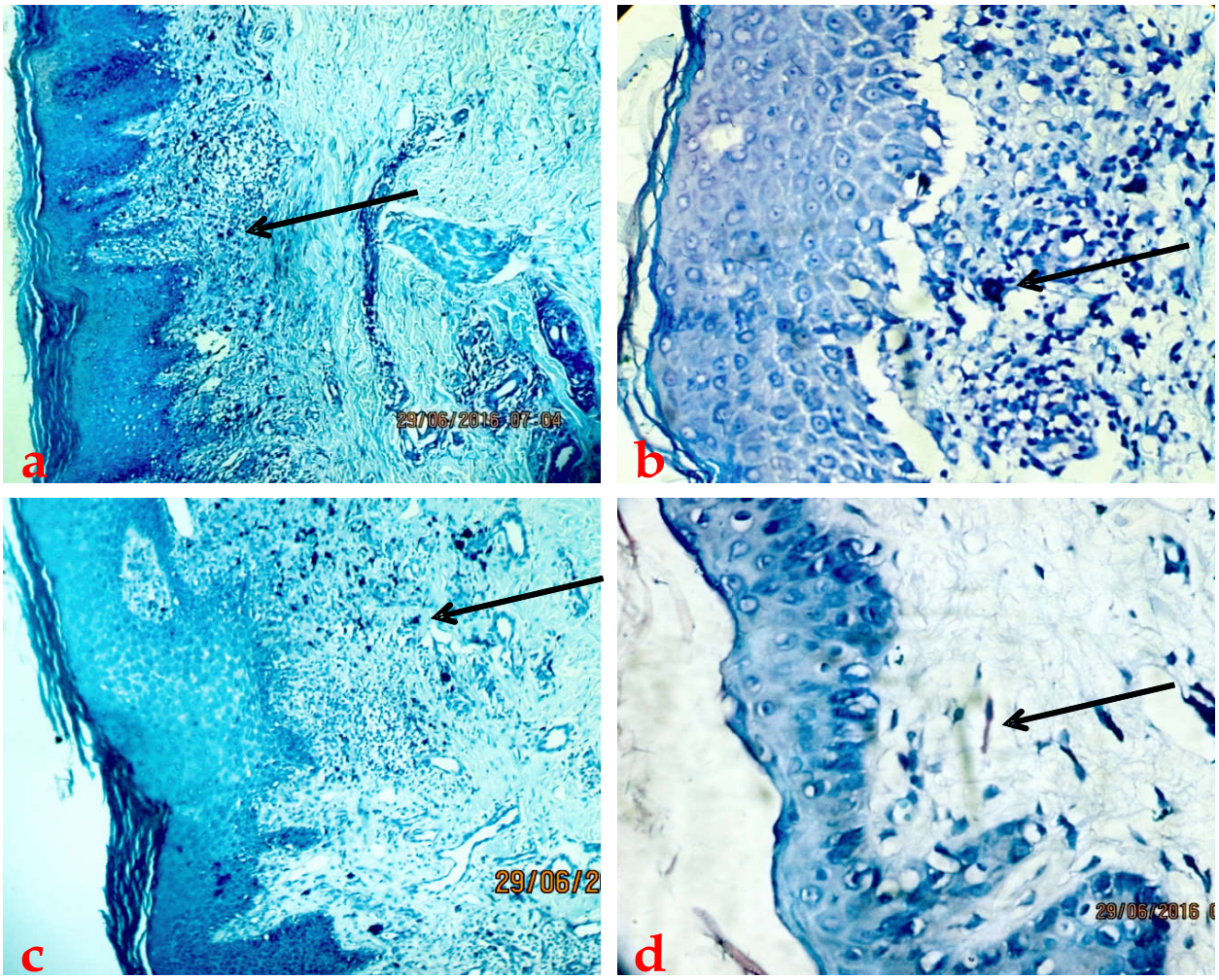

Fig. 1: a- Psoriasis vulgaris **b-** Lichen planus **c-**Lichen simplex chronicus and **d-** Lichen amyloidosis with mast cells (arrows) (Toludine blue, X400)

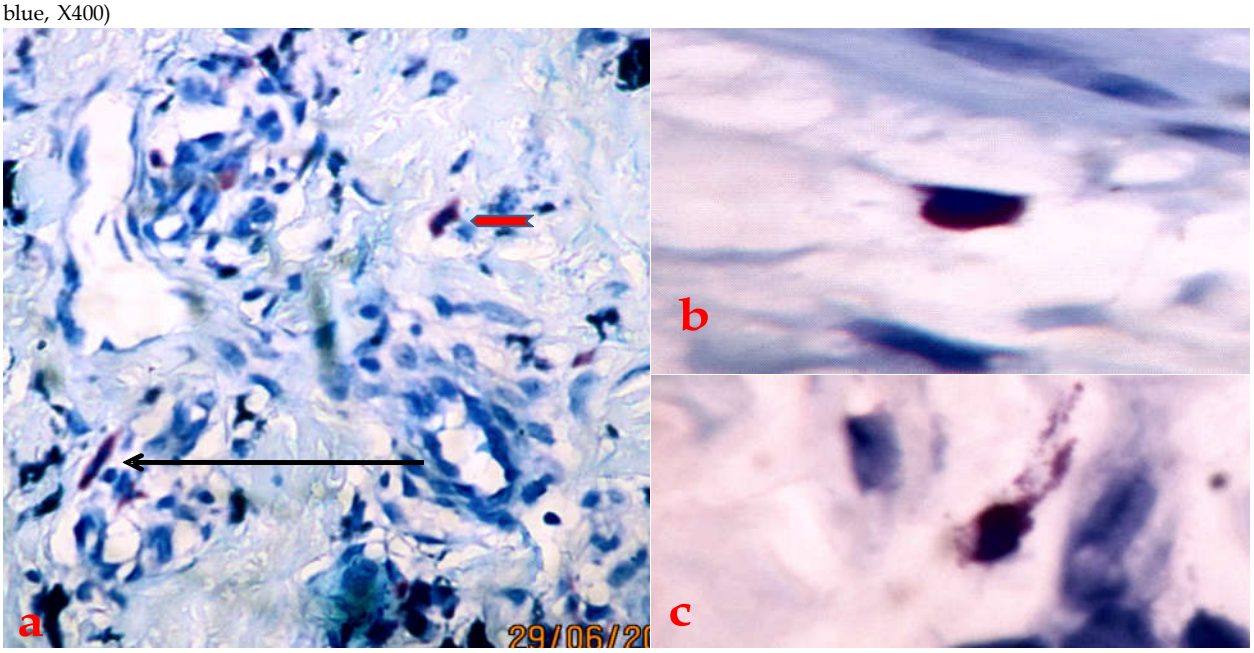

Fig. 2: a-Perivascular location of spindled (arrow) and round mast cells (arrowhead) (Toludine blue, X400) **b-** Round granulated mast cell (Toludine blue, X400) **c-** Degranulated round mast cell (Toludine blue,X400)

Discussion

Mast cells are commonly distributed at the sites of interface between external environment and host such as skin, respiratory and gastrointestinal mucosa. This distribution endows them with the potential to react to environmental stimuli as first responders. In the subepithelium, the mast cells surround blood vessels, nerves, smooth muscles, mucus glands and hair follicles [1-9]. This strategic localization allows them to play role in homeostatic process and function as primary immune barrier.

Three types of mast cells have been described based on their granule content – Mast $cell_{T,}$ Mast $cell_{C}$ and Mast $cell_{TC}$. MC_{T} store tryptase, whereas MC_{TC} release tryptase, chymase and carboxypeptidases.MC_{C} granules show chymase and carboxypeptidase, but not tryptase [1,5]. MC_{T} are found in intestinal and pulmonary mucosa. MC_{TC} are found in skin and lymph nodes [1,8].

The mast cell phenotypic plasticity and variation in content of granules underlie the heterogeneity in sensitivity to activation and responses generated [1].

Mast cells are unique among immune effector cells in that progenitor cells are released from hematopoietic cell reserve. Homing of these progenitor cells to the site of inflammation is directed by interaction of integrin expressed on these progenitor cells with adhesion molecules of endothelial cells such as VCAM-1. Stem cell factor, IL-6, IL-33, Neurotrophin-3 and Nerve Growth factor promote growth, maturation and survival of mast cells. Despite being differentiated cells, mast cells retain the ability to transdifferentiate and proliferate [1,2,5,8]. Mast cells have the ability to store proteases, histamine and several cytokines in their granules. These mediators exhibit distinct functions in diverse circumstances. Mast cells have been implicated in diverse pathologies such as arthritis, angiogenesis, glomerulonephritis, immune defense, allergic airway inflammation and aneurysm formation [1,2].

Apart from the most described method of activation mediated by IgE receptors, the mast cells are also stimulated by microbes, neuropeptides, cytokines, growth factors, toxins, basic compounds, complement, immune complexes, certain drugs, lectins,cytokines, stress hormones, chemokines as well as physical stimuli. Mast cell also participate in neuroimmune interaction with neurons through protease activated receptors [1,3,8,10]

On light microscopy, mast cells were recognized as round or elongated cells, 8-20 μm in size, having a monolobed round nucleus and cytoplasmic metachromatic granules. However lymphocytes, histiocytes, nevomelanocytes, monocytes are morphological simulators which justify the use of metachromatic staining property of toludine blue.[7] Metachromasia is due to interaction of basic dye to acidic residues on highly sulfated glycosaminoglycan chains attached to serglycin, a proteoglycan distributed in mast cell granules. The gold standard method of identification of mast cells on section is staining with anti-tryptase monoclonal antibodies [1,11].

Mast cells release diverse mediators by exostosis, degranulation or differential mediator release. Exocytosis encompasses fusion of granule membrane and plasma membrane with resultant massive release of all preformed mediators as exemplified in IgE mediated allergic reactions. Slow selective release of mediators without membrane fusion events characterizes differential release [2,5,8].

We have demonstrated the presence of mast cells in various papulo-squamous lesions. A review of their pathogenetic role in causation of the commoner lesions follows.

Presence of mast cells in close association with psoriatic epidermis is well recognized. All the cases of Psoriasis in our study showed mast cell in perivascular region of superficial papillary dermis (Figure 2a). Degranulated mast cells appear around post capillary venules in early psoriatic lesions [8,10]. Following degranulation, tryptase and other proteases released promote inflammation [10]. Chemokines and chemoattractants such as SCF, TGF-β, RANTES and stromal cell derived factor-1α (CXCL-12) produced in the inflamed skin tissue can induce migration of mast cells to site of inflammation and thus explain mast cell accumulation. Tryptase secreted by mast cells promotes neurogenic inflammation by activating PAR-2 receptors on nerve ends and leading to release of neuropeptides like substance P [5]. Increased number of neuropeptide containing sensory nerves and mast cells are seen in psoriasis. Mast cell and nerve fibre contacts are more frequently found in psoriatic skin [8]. Such mast cell-neuronal interaction underlies exacerbation of symptoms by stress [8,12]. Mast cell tryptase is able to activate metalloproteases such as MMP-3 and MMP-9, which degrade basement membrane allowing intraepidermal migration of inflammatory cells characteristic of Psoriasis.[5,8] Munro's microabscess in stratum corneum and spongiform pustules of Kogoj in stratum spinosum are neutrophilic aggregates seen in psoriatic skin. Mast cells release IL-17 through extracellular traps and conventional degranulation can promote Th17

type neutrophil rich inflammation through its mediators [13]. Mast cells secrete VEGF to induce angiogenesis, thence contribute to increased subepidermal vascularity [5,8]. IL-17, TNF-α and IFN-γ released by extracellular traps or degranulation induce keratinocyte proliferation and release of mediators, leading to a positive feedback loop. Small molecule inhibitors of IL-17 and TNF-α are deemed highly effective in treatment of psoriasis [14]. Mast cell tryptase can activate epidermal cells through PAR-2 receptors [5]. TNF-α secreted by mast cells stimulate T cells. T lymphocytes are common composition of cellular infiltrate in psoriasis. Petersen LJ et al found decrease in number of lymphocytes and amount of histamine release to secretagouges in psoriatic skin lesions following treatment with ranitidine. Hence, the authors postulated that lymphocyte derived cytokines modify the release of mast cell mediators [8,10]. Mast cell density decreases progressively with age of lesion and treatment [7]. Increased interstitial histamine concentration in psoriatic skin suggests increased selective mast cell degranulation [5,8]. Cyclosporin A is a potent immunomodulator used in treatment of psoriasis. Efficacy of cyclosporine A can be attributed to inhibition of mast cell activity and decrease in mast cell number [8].

Lichen simplex chronicus is histologically characterized by hyperkeratosis, psoriasiform hyperplasia, dermal chronic inflammation and fibrosis. It is also termed neurodermatitis. LSC is a prototype of atopic dermatitis. Mast cell secretes cytokines which can initiate inflammation mediated by Th 2 cells. Such an immune response is commonly associated with atopic dermatitis [5,7]. Mast cell products such as histamine, heparin, IL-4, TNF-α are mitogenic for fibroblasts and endothelial cells. Hence, increased mast cells is associated with fibrosis and angiogenesis [7]. Degranulation of mast cells correlates with increase in synthesis of type αl (I) procollagen mRNA [15]. Fibroblast proliferation and collagen deposition under the influence of mast cell fibrogenic cytokines result in vertically oriented collagen in papillary dermis characteristic of Lichen simplex chromicus [7]. Lichen amyloidosis is a proposed variant of lichen simplex chronicus wherein amyloid derived from necrosed keratinocytes is seen in dermis [7]. Increased granulated Mast cells were seen on toludine section (Figure 2b).

The presence of increased mast cells in psoriasis, lichen simplex chronicus and lichen amyloidosis in our study provides corroborative evidence to link them pathogenetically.

Many studies like Sharma R et.al, Ismail S et al, Spoorthi et al and Sugarman et.al have reiterated the role of mast cells in pathogenesis of Lichen planus [4,16-18]. Zhao et.al reported that mast cell density was higher in oral lichen planus lesions [19]. Zhao et.al reported that 60% of the oral lichen planus lesions showed degranulation in comparison to 20% of the cases of buccal mucosa [20]. Similarly, the present study reported degranulation in about 88% of the cutaneous lichen planus cases (Figure 2c). Lichen planus is a chronic inflammatory skin disease with characteristic clinical and histological features. An autoimmune reaction mediated by cytotoxic CD8+ T cells induced apoptosis of basal keratinocytes is presumed to underlie its pathogenesis [4,21]. Mast cells play a role in epithelial membrane disruption in oral lichen planus which will allow CD 8+ T cells to migrate through the basement membrane to enter epithelium [18]. Lichen plano pilaris and Lichen planus pigmentosus are the peculiar clinical variants of Lichen planus distinguished by topographic distribution. All the variants share similar histology [22]. The connective tissue mast cells help in recruitment of inflammatory cells resulting in the characteristic inflammatory band [4]. Up regulation of the endothelial cell adhesion molecules like CD 62E, CD54 and CD 106, which is required for lymphocyte adhesion to the luminal surfaces of blood vessels occurs due the release of the TNF-α [23–25]. A bidirectional interaction exists between T lymphocytes and Mast cells to maintain chronicity of the lesion [4]. TNF-α upregulates lesional T cell RANTES (Regulated upon Activation, Normal T cell Expressed and Secreted) which provides a mechanism of accumulation and activation of mast cells in lichen planus lesions. The consequence of which leads to mast cell degranulation [20].

A few mast cells were found in the case of Pityriasis Lichenoides et varioliformis acuta (PLEVA). Accumulation of neutrophils and eosinophils in guinea pig skin, following tryptase injection has been demonstrated in animal models. Neutrophil recruitment as seen in PLEVA is promoted by TNF-α and MIP-2 secreted by mast cells. Mast cell can promote neutrophil Th17 cell dependent in vivo [5].

Both perivascular and randomly localized mast cells were seen in our cases of DLE. Chymase detaches keratinocytes from substratum and can induce blister formation in discoid lupus erthyematosus [5].

The histological features of Rosacea include angulated telangiectasia, polymorphous perivascular infiltrate and dermal edema. Increased dermal mast cells are also a main feature in both of our cases. Mast cells and their mediators can lead to all of the typical features [26].

Conclusion

Mast cells are multifunctional cells implicated in pathogenesis of several chronic inflammatory disorders, autoimmune diseases and cancers [1]. Mast cell density, morphology and distribution in the present study provided support in understanding pathogenesis and evolution of few papulosquamous lesions. Mast cell release plethora of preformed and newly synthesized mediators which enable to play a role in pathogenesis of multiple skin lesions. Once dismissed as allergy cell, role of mast cells in psoriasis has become obvious now. With the expanded role of Mast cell it is apt to be addressed as Master cell [3].

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