661

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THE GEOGRAPHICAL DISTRIBUTION OF MAST CELL SUBTYPES IN PAINFUL BLADDER SYNDROME/INTERSTITIAL CYSTITIS: IMPLICATIONS FOR PATHOGENESIS

Hypothesis / aims of study

Painful bladder syndrome/interstitial cystitis (PBS/IC) is a chronic inflammatory disorder of the urinary bladder. Although the pathogenesis of PBS/IC is not fully understood, it is thought to be related to the activation and proliferation of inflammatory cells in the bladder [1]. Specifically mast cell proliferation within the muscle layer (detrusor) of the bladder wall is considered to be the cause of PBS/IC in at least a subset of sufferers [2]. However, there are few scientific studies investigating the role of mast cell subtypes in PBS/IC. The aim of this study was to use immunohistochemimical and imaging techniques to identify and compare the location of mast cell subtypes (tryptase-positive and chymase-negative mast cells (AA1) *vs* trypase-positive and chymase-positive mast cells (CC1)) in bladder tissue specimens of PBS/IC. Differences in the location and density of mast cell subtype populations were explored in order to identify any impact of geographical variation in regards to the pathogenesis and diagnosis of PBS/IC.

Study design, materials and methods

Ethical approval was granted for the study. Informed consent was sought from all participants and the relevant clinical details were collected. Full-thickness bladder tissue was collected from patients with PBS/IC (n=14) and from patients with normal histological findings (n=4). Samples were paraffin-embedded and sectioned for immunohistochemistry. Mast cell subtypes were stained using anti-mast cell tryptase antibody (AA1), and anti-mast cell chymase antibody (CC1). Slides were photographed at x20 magnification using the dotSlide Olympus microscopy system, and positively stained mast cells were quantified using ImageJ software (Figure 1).

Results

There was a significant difference in the density of mast cells between each layer of the bladder wall in PBS/IC tissue, with the greatest accumulation of mast cells found within the detrusor layer ($p<0.05$; Figure 2). There was no statistically significant difference in the density and location of mast cell subtypes within histopathologically normal bladder tissue (Figure 3). A similar pattern of distribution was seen with chymase mast cells (CC1-positively stained). This was statistically significant for detrusor ($p<0.01$) and the lamina ($p<0.01$) layers (Figure 4).

Interpretation of results

The statistically significant increase in mast cell density within the detrusor muscle layer of PBS/IC individuals may be attributed to the presence and increase in inflammatory cytokines that recruit and activate mast cells, one such cytokine is the Stem Cell Factor (SCF) [3]. Within the PBS/IC bladder, this key cytokine is expressed by smooth muscle cells and damaged urothelial cells, and is a key inflammatory cytokine for the maturation and differentiation of mast cells [3]. In addition, activated mast cells will release various factors such as Substance P [3]. Thus, the mastocytosis, specifically, detrusor muscle mastocytosis, seen in this study is explained by the self-perpetuating cycle of mast cell activation and recruitment. The results also indicate that there is no significant difference in the density of mast cell subtypes in control tissue and they are equally represented in each layer of the bladder wall being maximal in the detrusor compartment. When comparing CC1 positive mast cells it should be noted that the number of mast cells within the adventitial layer is almost identical between normal controls and PBS/IC bladder.

Concluding message

Our results showed that the increase in the number of mast cells in PBS/IC is mainly due to the tryptase-positive and chymase-negative subtype (AA1) and the influx of mast cells seen in the detrusor layer of PBS/IC individuals is also mostly due to the tryptase-positive and chymase-negative (AA1) subtype. The significant increase of the tryptase-positive chymase-positive (CC1) subtype in the detrusor and lamina layers of PBS/IC individuals is an interesting finding, hence chymase is regarded to have a greater destructive potential than tryptase, and the presence of chymase in some individuals may explain the variability in severity of symptoms between PBS/IC sufferers. These findings may provide new insight into the role of mast cells in PBS/IC, further our understanding of the pathogenesis of the disease, and help develop novel treatment strategies for this debilitating disorder.

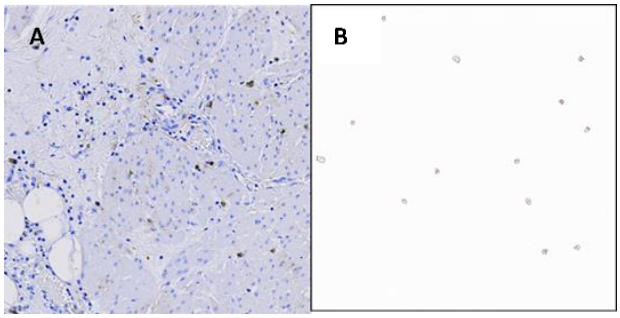

Figure 1: A) The detrusor muscle layer positively stained for mast cell tryptase with the AA1 antibody (brown). B) The "skeleton" left after the image has been processed by ImageJ.

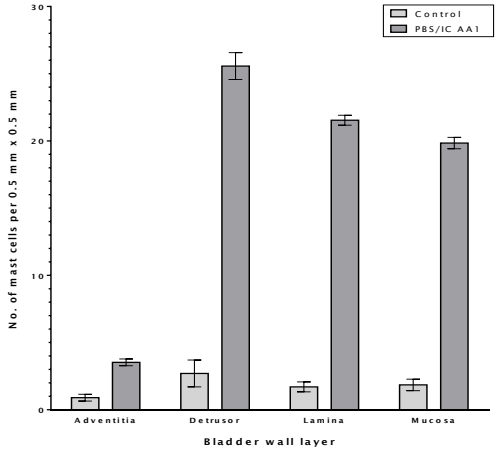

Figure 2: The mean no. of AA1-positively stained mast cells within the bladder wall of PBS/IC individuals and control individuals. (±SEM).

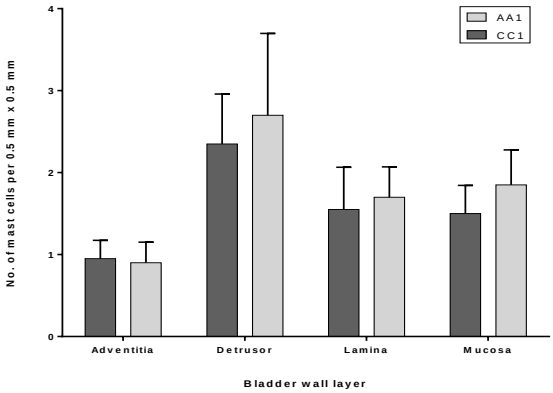

Figure 3: The mean no. of AA1 positively stained mast cells in comparison to CC1-positively stained mast cells in control individuals. (±SEM).

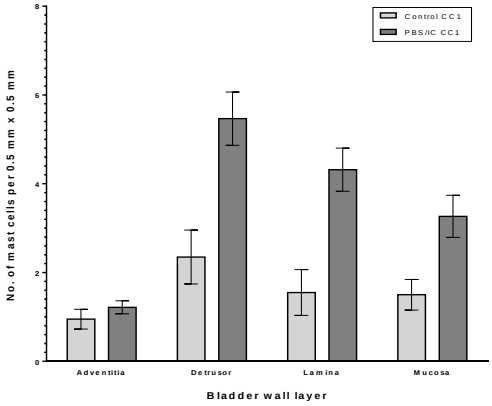

Figure 4: The mean no. of CC1-positively stained mast cells within the bladder wall of PBS/IC individuals and control individuals (±SEM).

References

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3. None declared.

Disclosures

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