Commentary

Mast cell activation syndrome

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It has been over 30 years since the Interstitial Cystitis Association of America (ICA) was established in 1984. Although a great deal more is understood about interstitial cystitis/bladder pain syndrome (IC/BPS), the cause and cure of this condition remains unknown. One hypothesis regarding etiology that appears to have been overlooked or dismissed is a theory that involves mast cells. It is worthwhile taking a second look.

Mast cell activation syndrome (MCAS)

Mast cells are found in all tissues of the body and are typically in close proximity to blood vessels and nerves. "The clinical presentation of MCAS is very diverse, due to both the widespread distribution of mast cells and a great heterogeneity of aberrant mediator expression patterns, (therefore) symptoms can occur in virtually all organs and tissue" (1). When mast cells degranulate, there are a wide range of inflammatory mediators released in various combinations. These include histamine, heparin, proteases, tryptase, cytokines such as TNF alpha, certain prostaglandins, leukotrienes and many others (1-4). In fact, there are over 200 inflammatory mediators that have been identified thus far. MCAS is distinct from mastocytosis in that it does not include the entire body, but may involve a specific organ, such as the bladder or GI tract. It is a condition of inappropriately activated mast cells (5). If MCAS does play a role in IC/BPS, the number of mast cells on bladder biopsy may be increased in IC/BPS patients or the mast cell population may not be increased, but may be hyper-responsive and degranulate more frequently in response to a trigger stimuli. It is also possible that mast cells may release inflammatory mediators without degranulation of the mast cell (1-3). Genetic abnormality is likely to play a role as well (5).

To date, I am not aware of any large-scale study that compares the number of mast cells in the bladder biopsy of IC/BPS patients versus the number of mast cells in patients with a normal bladder biopsy using up-to-date staining techniques. H&E staining is the typical stain used in the pathology lab, which is not adequate to identify the correct number of mast cells on biopsy. Some urologists request the use of tryptase or toluidine blue, and while this improves accuracy, the most sensitive and accurate stain available today is CD-117 (2).

In the bladder, mast cells are in close proximity to neurons, as they are in all areas of the body. They all communicate with each other. Mast cells can both degranulate as well as transgranulate via the formation of filipodia (thin, finger-like projections) that attach directly to the neuronal membrane (6). The inflammatory mediators, once released into the bladder could initiate urgency, frequency, supra-pubic pressure and pain of varying degrees. This would depend on the number of mast cells that degranulate, those that release inflammatory mediators without degranulation, the type of inflammatory mediators released, and/or mast cells that are normal in number but are hyper-responsive and degranulate more frequently. Transgranulation has already been shown to occur in the normal bladder *in vivo* (7). Via transgranulation, mast cell inflammatory mediators are taken up directly by the nerve via endocytosis and released into the cytoplasm of the nerve, or found in membrane-bound organelles within the nerve (6). This could trigger pain fibers in the bladder and the electrical impulses would then travel via the ascending pain pathway from the bladder to the spinal cord and on to the central nervous system (CNS), targeting the limbic system, thalamus and cortex.

In the CNS, transgranulation has been shown to

occur as well (6), but what role the mast cell fragments play within the CNS is unclear (8). The phenomenon of transgranulation in the CNS has been found in both normal and diseased states. (6,8). This could be the case in other organs as well. However, we are primarily looking at mast cells in the bladder and mast cell degranulation in this case, with transgranulation providing a pain pathway to the CNS from local symptoms in the bladder.

Mast cells and mast cell degranulation may provide a useful way of evaluating patients who likely have IC/BPS. Products of mast cell degranulation in the urine, for example histamine, N-methylhistamine and others, can be extremely difficult to measure because of their short half-lives. This may contribute to false negative results. However, accurate testing of many urinary inflammatory mediators have been successfully measured (3) and objective findings could yield results that might:

(I) Explain the etiology or an etiology of IC/BPS;
(II) Provide diagnostic testing, and/or a marker for the condition;
(III) Provide treatment directed at the specific inflammatory mediators found to be abnormally high;
(IV) Reduce the amount of time to diagnosis, and possibly categorize the disease.

Measuring the number of mast cells in the biopsies of IC/BPS patients and controls using the stain CD-117 is a relatively simple trial that could be easily undertaken. Inflammatory mediators should then be measured in the urine of both IC/BPS patients and controls to further evaluate the potential differences between these two groups. If there appears to be no difference between the two groups, next steps should include use of an electron microscopy using time lapse photography on bladder biopsies from IC/BPS patients and controls to see if the mast cells in the biopsies of IC/BPS patients are degranulating at a more frequent rate, or releasing inflammatory mediators without degranulating compared to the control group.

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Footnote

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