Dear editors,

In the short article by Prof. Ratner on mast cell activation syndrome and its overlooked or dismissed possible contribution to bladder pain syndrome/interstitial cystitis (BPS/IC) (1), the author outlines that increased numbers of activated mast cells (mast cell activation syndrome) may play a role in the development of painful BPS/IC. This association has been long recognized by the European Society for the Study of Interstitial Cystitis (ESSIC) which proposes mast cell counts in the detrusor muscle with a density >28 mast cells/mm$^2$ as diagnostic criterion for BPS/IC (2). Mast cells, however, are found in all tissues and organs, and can be increased and activated due to a number of stimuli and in numerous diseases. Prof. Ratner claims that she is not aware of large scale studies that compare the number of mast cells in biopsies of BPS/IC and a normal control group and therefore proposes a simple comparative study with antibody to CD117. I like to draw attention to our study published last year (3). In this study lead by Dr. Marianne Gamper and Prof. Volker Viereck, we evaluated patients from the Department of Gynecology, Kantonsspital Frauenfeld, Switzerland. We compared the number and distribution of mast cells in biopsies of 56 patients with BPS/IC with and without Hunner’s lesion, overactive bladder and normal control patients. Many biopsies did not contain enough amounts of detrusor muscle for evaluation according to ESSIC, but increased mucosal mast cells were found in all 4 patient groups. Mast cells at a density >32 mast cells/mm$^2$ in the detrusor muscle and particularly the location beneath the urothelium were statistically significant and typical for BPS/IC with Hunner’s lesion. The other patient groups showed increased mast cells in a diffuse distribution with sparing of the suburothelial stroma. A review of concomitant diseases revealed that patients throughout all groups suffered from numerous diseases associated with mast cell activation (allergies, asthma, atopy, food intolerances and autoimmune diseases), a possible explanation for the presence of a moderate mast cells (in the disease groups as well as the control groups). The difficult clinical distinction on cystoscopy involves BPS/IC without Hunner’s lesions and OAB. Density of the mast cells alone was not able to differentiate BPS/IC without Hunner’s lesion from OAB, but a separation was possible in combination with the clinical symptom “pain” and the typical inflammatory infiltrate in biopsies of BPS/IC.

Detection of mast cells in tissue can be achieved by several methods (Giemsa stain, toluidine stain). Presently the most effective method is immunohistochemistry. The article proposed antibody for the comparative study was CD117, but we prefer to use an antibody to human mast cell tryptase. Antibody to CD117 stains mast cell membranes only. Antibody to human mast cell tryptase additionally stains granules and therefore allows determination of the activation state, e.g., if all mast cell granules are located within the cytoplasm (non-activated), or released and located outside the cytoplasm (degranulated, activated). Degranulation of mast cells may point towards a hyper-responsive state and patients may benefit from therapy with mast cell stabilizers. Patients with BPS/IC suffer from nociceptive and neuropathic pain. Mast cell products released after degranulation sensitize peripheral nociceptive nerve fibers in the respective organ, but other products, such as nerve growth factor, additionally participate in generation of chronic neuropathic pain with central pain.
processing in dorsal root ganglia and brain.

Mast cells have been implicated in a number of other pain syndromes including migraine, chronic pelvic pain, endometriosis, and vulvodynia. Vulvodynia is a poorly understood complex pain syndrome characterized by increased mast cells and sensory hyperinnervation which often coexists with BPS/IC (4). We made similar observations with respect to mast cell hyperplasia in patients with vulvodynia (5). Most biopsies contained >60 mast cells/mm² (range, 40–120 mast cells) in subepithelial distribution or clustering around the vestibular glands. The majority of mast cells showed activation, e.g., degranulation. About of 70% of vulvodynia patients had concomitant diseases with mast cell activation (infections, allergies to penicillin, food, animal hair, house dust mites, and atopy, extra-genital psoriasis, anti-phospholipid syndrome, idiopathic biliary sclerosis, fibromyalgia and histamine intolerance). Treatment is multimodal but also targets mast cells.

Increased uniform mast cell infiltrates (mast cell activation syndrome) are typically a benign process, but one should always keep in mind the possibility of an (indolent) malignant mast cell disease. Spindle cell shape, or aberrant CD25 expression may hint towards an atypical phenotype or underlying clonal mast cell disease as described in patients with the chronic lichenoid dermatosis lichen planus in genital skin (6).

Overall, there is agreement that mast cells play an intricate role in pain syndromes and in particular in BPS/IC. Mast cells participate early in disease development in nociceptive pain, e.g., by sensitization of nerve fibers. Mast cell products continue to perpetuate both acute and chronic pain, leading to the difficult-to-treat neuropathic pain. This situation makes mast cells an interesting therapeutic target.

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None.

Footnote
Conflicts of Interest: The author has no conflicts of interest to declare.

Comment on: Ratner V. Mast cell activation syndrome. Transl Androl Urol 2015;4:587-8.

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