Current Bladder Dysfunction Reports (2020) 15:1–8
https://doi.org/10.1007/s11884-019-00569-w

BPS/INTERSTITIAL CYSTITIS (D CASTRO-DIAZ AND Y IGAWA, SECTION EDITORS)

Update on the Pathophysiology of Interstitial Cystitis /Bladder Pain Syndrome

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Published online: 6 January 2020

Abstract

Purpose of Review Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic, potentially debilitating condition characterized by lower urinary tract symptoms and pain perceived to be related to the bladder. The etiology of IC/BPS has been rigorously studied for more than a century, but remains unknown. IC/BPS comprises a wide variety of clinical phenotypes with different potential etiologies. Recently, the importance of IC/BPS subtyping has become recognized. In this review, we revisit current hypotheses on IC/BPS pathophysiology and discuss the most likely causes of IC/BPS according to current research.

Recent Findings Recent histological and genomic analyses revealed that IC/BPS with Hunner lesions is a distinct inflammatory disorder characterized by epithelial denudation and frequent clonal expansion of infiltrating B cells, in association with biological processes involved in immune responses and infectious disease. Meanwhile, IC/BPS without Hunner lesions is an unrelated, non-inflammatory disorder with few histological changes, and which is potentially associated with systemic neurophysiological/endocrine abnormalities. Recent evidence has also cast doubt on the importance of features that have been conventionally considered significant in IC/BPS pathophysiology, such as mast cell infiltration or glomerulation.

Summary IC/BPS with Hunner lesions should be considered IC, and IC/BPS without Hunner lesions should be considered BPS. Clear and proper phenotyping of IC/BPS is necessary for the successful diagnosis and treatment of IC/BPS and to facilitate future research on IC/BPS pathophysiology.

Keywords Interstitial cystitis · Bladder pain syndrome · Pathophysiology · Infection · Immune response

Introduction

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a complex of chronic debilitating symptoms characterized by urologic chronic pelvic pain associated with lower urinary tract symptoms [1]. IC/BPS comprises a diverse variety of clinical phenotypes with different potential etiologies. However, precise subtyping of IC/BPS remains to be established due to its unknown etiology and the diverse sites and degrees of symptoms. Currently, one clear phenotype that has emerged is IC/BPS with Hunner lesions [the International Society for the Study of Bladder Pain Syndrome (ESSIC) criteria BPS type 3]. Recent evidence suggests that IC/BPS with Hunner lesions shows distinct features with respect to histology, gene expression, and prognosis compared with other forms of IC/BPS [2, 3••, 4]. IC/BPS with Hunner lesions is a robust inflammatory disorder characterized by epithelial denudation, pancystitis, and frequent clonal expansion of infiltrating B cells, with overexpression of genes involved in immune responses and infection [3••, 5••]. Meanwhile, IC/BPS without Hunner lesions is a distinct non-inflammatory disorder characterized by preservation of the urothelium layer and symptom spread beyond the bladder [2, 6•]. Thus, IC/BPS with and without Hunner lesions should be clearly distinguished, and the two should not be combined when evaluating the potential underlying pathophysiology or when designing clinical trials. Experts in the US emphasized this notion recently and suggested that past clinical trial failures and the persistent inconclusive results of basic research on IC/BPS might be attributable to the lack of proper phenotyping [7]. In this review, the potential etiologies of IC/BPS will be discussed with respect to IC/BPS phenotype.

This article is part of the *Topical Collection on BPS/Interstitial Cystitis*

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Potential Etiologies of IC/BPS

Urothelium Defects

Urothelial deficiency is generally considered a primary cause of IC/BPS [8]. Functional and/or quantitative loss of urothelial barrier function permits urinary subnoxious irritants to directly contact the suburothelial layer, resulting in inflammatory responses or afferent nerve stimulation [9].

As mentioned above, it is likely that quantitative loss of the urothelium plays a role in the etiology of IC/BPS with Hunner lesions, in which the urothelium is almost completely denuded at the lesion sites [2]. However, epithelial functional loss may occur in IC/BPS with and without Hunner lesions. The detailed mechanisms thought to contribute to this urothelium deficiency are as follows.

1. Abnormality of the glycosaminoglycan (GAG) layer of the urothelium

Parsons and colleagues suggested that abnormalities of the GAG layer might be associated with the urothelial dysfunction of IC/BPS [8]. The GAG layer, which consists of glycoproteins and proteoglycans, plays a pivotal role in protective barrier function [10]. Disruption of the GAG layer increases the permeability of the urothelial layer, leading to subepithelial inflammation and lower urinary tract hypersensitivity symptoms such as bladder/pelvic pain and urinary frequency [10]. The use of conventional intravesical therapies with GAG family components such as heparan sulfate, chondroitin sulfate, or hyaluronic acid is based on the rationale that replenishment of the GAG layer might promote urothelial layer recovery [11].

2. Impaired cell adhesion

Liu et al. reported that tight junction proteins such as E-cadherin and zonula occludens-1 (ZO-1) are downregulated in patients with IC/BPS compared with control patients or those with overactive bladder syndrome [12]. Interestingly, the subjects analyzed in that study all had IC/BPS without Hunner lesions. Montalbetti et al. demonstrated that, in rats, increased urothelial permeability caused by disrupted urothelial tight junctions led to bladder afferent nerve hyperexcitability and upstream central nerve sensitization with slight inflammatory changes, without altering epithelial quantity or umbrella cell polarity/differentiation [9, 13]. Impaired cell adhesion and increased urothelial permeability (e.g., not quantitative but functional disruption of the urothelium) may be associated with the pathophysiology of IC/BPS, especially IC/BPS without Hunner lesions.

3. Aberrant epithelial proliferation

Loss of epithelial cells due to altered production of antiproliferative factors or certain growth factors or increased apoptotic activity has been reported in IC/BPS [14, 15]. This hypothesis would implicate quantitative loss of epithelium in the etiology of IC/BPS with Hunner lesions.

4. Toxic substances in the urine

Parsons et al. suggested that cationic urinary components could potentially be cytotoxic to urothelial cells, leading to bladder mucosal injury [16]. It is also well known that ketamine-induced cystitis resembles IC/BPS with Hunner lesions both histologically and clinically [17]. Although the detailed etiology of ketamine cystitis has not been clearly elucidated, direct damage to the urothelium by urine metabolites of ketamine has been suggested as a possible mechanism [17]. In IC/BPS with Hunner lesions, urine itself also seems to exacerbate the hypersensitivity symptoms by leaking into the bladder subepithelial layer at the lesion sites, where the full layer of urothelium is frequently sloughed off [2]. It is well recognized that there is an association between diet and symptom severity in IC/BPS [18–20]. In routine clinical practice, we find that patients with IC/BPS with Hunner lesions often notice a relationship between intake of specific foods and worsening symptoms. Alterations in the osmolarity, composition, or acidity of the urine due to the consumption of specific foods may stimulate the peripheral afferent nerves in the bladder, in addition to the direct cytotoxic effects of dietary metabolites, medications, or dietary supplements on the urothelium [21–23•]. Given this aspect of symptom triggering in IC/BPS, the responsiveness of the Hunner lesion-targeted therapies is reasonable. [4]

5. Autoimmunity against the bladder urothelium

Specific autoantibodies have not been identified in IC/BPS, although non-specific anti-nuclear antibodies have been reported in some cases [24–27]. However, the clinical manifestations of patients with bladder disorders associated with other systemic autoimmune diseases such as Sjogren's syndrome, systemic lupus erythematosus, or autoimmune thyroiditis are quite similar to those of patients with IC/BPS with Hunner lesions [28, 29]. Deposits of immunoglobulin and complement are observed in the bladders of patients with systemic autoimmune disorders with urinary symptoms as well as in patients with IC/BPS [27, 30, 31]. In patients with IC/BPS with Hunner lesions, epithelial denudation and lymphoplasmacytic infiltration of the bladder are observed, with frequent clonal expansion of infiltrating B cells [5••]. These findings strongly imply that autoimmune responses underlie the pathophysiology of IC/BPS with Hunner lesions. In

an animal model of autoimmune cystitis induced by immunization with uroplakin and in transgenic mouse model that expresses antigenic ovalbumin (OVA) in the urothelium and OVA-specific receptor on CD8-positive T cells, mice spontaneously develop a form of cystitis that strongly resembles IC/BPS with Hunner lesions in histology and lower urinary tract hypersensitivity symptoms [32–34].

Inflammation

Activation of Mast Cells

Mast cell infiltration has been also considered a characteristic feature of IC/BPS [35–41]. Before the year 2000, Giemsa staining, toluidine blue staining, periodic acid-Schiff staining, and immunohistochemistry against c-kit were routinely used to identify mast cells. However, these staining methods are not specific for human mast cells [36, 40, 41]. In the 2000s, when an anti-tryptase antibody specific for human mast cells was developed [42], growing evidence cast doubt on the significance of mast cell infiltration in IC/BPS [43, 44••, 45••]. For example, we compared mast cell densities in the bladders of IC/BPS patients (with and without Hunner lesions) with those of non-IC controls (non-IC cystitis and normal bladder, respectively). A similar degree of background lymphoplasmacytic infiltration was observed in each pair (IC/BPS with Hunner lesions vs. non-IC cystitis, or IC/BPS without Hunner lesions vs. normal bladder). These results indicated that mast cell densities did not differ between IC/BPS and controls with equal background inflammation [45••], which suggests that mast cell infiltration may not be a specific histological feature of IC/BPS. In addition to the quantitative analysis, functional assessment of mast cells in IC/BPS should be performed in order to more firmly establish the role of mast cell infiltration in IC/BPS.

Immunologic Inflammation

Deposits of immunoglobulin and complement, and increased expression of the chemokine receptor CXCR3 and its ligands (CXCL9, 10, and 11), have been reported in the bladders of IC/BPS with Hunner lesions [27, 31, 46, 47]. Recently, we found that frequent expansion of light chain-restricted B cells was observed in the bladders of IC/BPS patients with Hunner lesions (Fig. 1) [5••]. This evidence collectively suggests that specific immune responses such as autoimmune responses may underlie the pathophysiology of IC/BPS with Hunner lesions.

In this context, the higher prevalence of comorbid autoimmune disorders in patients with IC/BPS with Hunner lesions may reflect this disease property [48, 49]. Potential pathogenic antigens, e.g., self-antigens in the bladder tissue or exogenous antigens such as those derived from microorganisms or chemical substances in the urine, are worth evaluating in the future. Our recent whole transcriptome analysis indicated that biological pathways related to the immune system and infectious disease were significantly enriched in IC/BPS with Hunner lesions [3••]. These results suggest that autoimmunity in conjunction with infection may underlie the pathophysiology of IC/BPS with Hunner lesions. However, specific autoantibodies have not been identified in IC/BPS, as mentioned above. Furthermore, the inefficacy of antibiotics and the lack of detection of pathogenic microorganisms by urine culture or bacterial DNA sequencing have cast doubt on bacterial infection as a potential etiologic factor in IC/BPS [50–53]. On the other hand, it has been reported that female IC patients had a higher prevalence of positive urine cultures [50, 54] and alterations in the diversity of urine bacterial flora [55, 56]. Patients with IC/BPS with Hunner lesions also had a higher frequency of Epstein-Barr virus infection [57], suggesting that microorganism infection might play a role in the pathogenesis of IC/BPS. Further studies on the relationship between immunologic inflammation frequently accompanied by B cell clonal expansion and microorganism infectionmay yield clues into the pathophysiology of IC/BPS.

Neurogenic Inflammation

Neurochemical transmitters can stimulate the afferent nerves or induce stromal inflammatory changes such as fibrosis or edema in the bladder. This process is mainly mediated by mast cells. Granules released by mast cells containing inflammatory mediators such as histamine, serotonin, tryptase, tumor necrosis factor (TNF)-α, or nerve growth factor (NGF) can stimulate the peripheral nerves in the bladder mucosa, which then release neuropeptides such as substance P and calcitonin gene-related peptide (CGRP) that further exacerbate mast cell degranulation (the nerve-mast cell interaction axis) [58–66]. As a consequence, chronic stimulation of the afferent nerves could lead to altered neural plasticity or central nerve sensitization in the dorsal root ganglia or the upper spinal cord, which may contribute to symptom persistence in IC/BPS [67]. Chitinase-like protein (YKL-40), another protein contained within mast cell granules, promotes stromal edema and fibrosis [68]. Mast cells are involved in diverse pathophysiological processes, such as synthesis of proinflammatory cytokines, recruitment of leucocytes, and vascular remodeling [69]. However, again, recent evidence has cast doubt on the significance of mast cells in IC/BPS pathophysiology. Gamper et al. reported that the degree of mast cell degranulation as well as mast cell numbers did not differ significantly between patients with IC/BPS and overactive bladder and non-IC controls without bladder pain [44••]. The role of neurogenic inflammation in IC/BPS should be revisited to take the proper IC/BPS phenotyping and control setting into account.

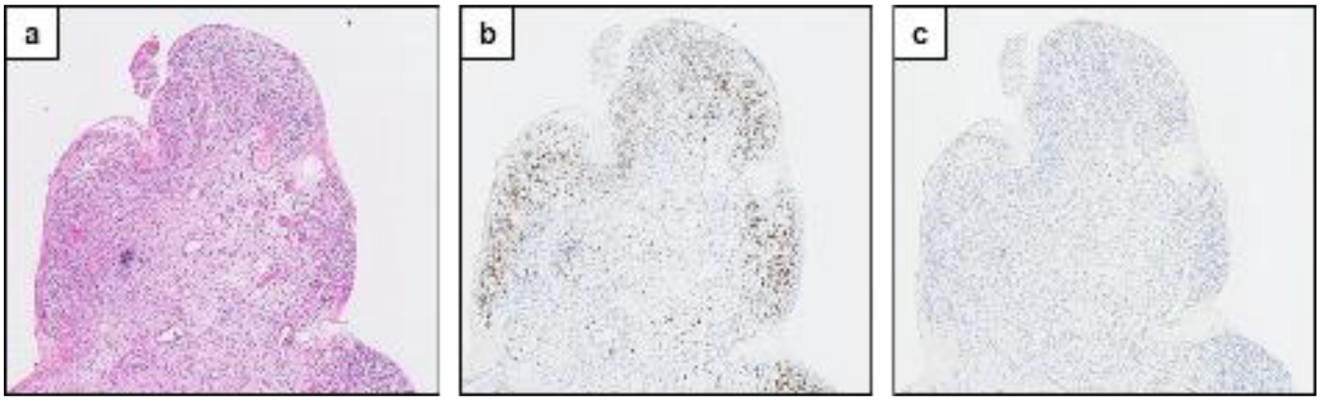

Fig. 1 Light chain restriction in infiltrating plasma cells in the bladder of IC/BPS with Hunner lesions. **a** Hematoxylin and eosin staining shows dense inflammatory infiltrates in the subepithelial layer. **b**, **c** In situ hybridization for the kappa chain (**b**) or lambda chain (**c**). Most plasma cells express the kappa chain

Increased Nociceptive Reflux Pathways

Increased gene expression of transient receptor potential channels (TRPs) and certain chemokines has been reported in IC/BPS with Hunner lesions [70]. These findings may reflect the increased activation of nociceptive reflux pathways in IC/BPS, possibly as a result of chronic inflammatory processes. On the other hand, the severity of symptoms in IC/BPS without Hunner lesions is similar to that in IC/BPS with Hunner lesions despite the absence of bladder inflammation. Other aberrant sensory pathways that could lead to central sensitization may underlie the pathophysiology of IC/BPS without Hunner lesions.

Increased Angiogenesis in the Urothelium

Increased angiogenesis is considered another pathogenic feature of IC/BPS [71]. Glomerulation (mucosal bleeding after bladder overdistension), which is considered a specific diagnostic marker of IC/BPS, could be associated with increased angiogenesis in conjunction with epithelial dysfunction [72, 73]. The angiogenetic factor most frequently reported to be increased in IC/BPS is vascular endothelial growth factor (VEGF), a proinflammatory growth factor that induces neovascularization and is involved in the pathogenesis of many chronic inflammatory disorders [74–76]. The elevated VEGF expression in IC/BPS with Hunner lesions is therefore likely a consequence of chronic inflammatory responses. However, our recent whole transcriptome study and quantitative microvascularity analysis failed to detect any significant difference in gene expression profile, biological pathways, microvessel density, VEGF expression, or subepithelial inflammation in patients with IC/BPS without Hunner lesions, regardless of the presence or absence of glomerulations [3••]. Further, a recent study questioned the connection between glomerulations and IC/BPS [77•]. Although it cannot be completely ruled out, the role of glomerulations in IC/BPS pathophysiology is currently unclear.

IC/BPS Without Hunner Lesions as a Potential Somatoform Disorder

A recent study reported that increased bladder capacity was associated with a set of psychological factors such as dissociative pathology and childhood relational trauma in patients with IC/BPS. These psychological factors are thought to underlie somatoform disorders and functional somatic syndromes (FSSs) [78, 79]. It is well known that patients with IC/BPS without Hunner lesions usually retain their bladder capacity significantly larger than those with Hunner lesions, and their symptoms frequently extend systemically (beyond the bladder) [6•, 80••]. Chen et al. indicated that somatic symptoms could potentially be linked to biological pathways that increase the risk of IC/BPS without Hunner lesions [81]. Warren et al. pointed out that there is strong overlap between the symptoms and comorbidities of IC/BPS without Hunner lesions and those of FSSs, including irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, and migraines [80••]. Patients with IC/BPS without Hunner lesions have all the characteristics and meet all the proposed criteria of a FSS [82••]. This evidence suggests that IC/BPS without Hunner lesions may share its neurophysiological process with widely recognized FSSs such as chronic fatigue syndrome, irritable bowel syndrome, and fibromyalgia, which lead to central sensitization [83]. The underlying pathophysiology of FSSs remains unclear, but aberrant neuroimmune or endocrine processes with certain stressors have been suggested [84]. A multidisciplinary approach (behavioral, biomedical, and cognitive) is appropriate for the treatment of IC/BPS without Hunner lesions.

Conclusions

Recent growing evidence has changed the current thinking on IC/BPS. IC/BPS with Hunner lesions is an inflammatory disease potentially associated with immune responses and infection, and should be considered distinct from the broad IC/BPS syndrome umbrella. Meanwhile, IC/BPS without Hunner lesions is a non-inflammatory disorder that is often associated with systemic hypersensitivity, potentially due to neurophysiological/endocrine abnormalities. Few bladder histological findings are noted in IC/BPS without Hunner lesions. This subtype may share the pathogenesis of widely recognized FSSs. Clear and proper phenotyping of IC/BPS will improve its clinical management, as the successful treatment of IC/BPS with Hunner lesions (IC) could be dependent on Hunner lesion-targeted therapies, while the treatment of IC/BPS without Hunner lesions (BPS) could require strategies similar to those used for the treatment of other somatic syndromes. Considering IC and BPS patients separately will also facilitate future research on IC/BPS.

Compliance with Ethical Standards

Conflict of Interest The author declares that there are no conflicts of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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- •• Of major importance

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