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

Classification, Characterization, and Sub-Grouping of Interstitial Cystitis

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Abstract

Purpose of Review Interstitial cystitis (IC) and IC-related conditions such as painful bladder syndrome (PBS), bladder pain syndrome (BPS), and hypersensitive bladder (HSB) have a similar symptomatic profile but probably different etiologies. A reasonable classification of these diseases/conditions is mandatory for clinical and investigational progress. We reviewed definition of current terminology and recent research evidence regarding IC and related conditions to propose a sensible classification system.

Recent Findings The condition with Hunner lesions (Hunner type IC: HIC) is obviously distinct from other categories in terms of histopathology, gene expression, and clinical management; HIC is a bladder-centric disease with heavy inflammation, epithelial denudation, and oligoclonal B cell expansion. Presence of glomerulations or mucosal bleeding after distension appears of least clinical significance. Classification should thus clearly differentiate the condition with Hunner lesions from those without Hunner lesions. The term covering patients as a whole should contain IC, since IC is historically a well-known name and used for insurance reimbursement.

Summary The proposed classification/taxonomy features an umbrella term (IC/BPS) and two sub-groups, HIC (IC/BPS with Hunner lesions) and BPS (IC/BPS without Hunner lesions). IC/BPS is convenient for the initial management of symptomatic patients, and sub-groups can categorize the patients for the specific management. The characteristic symptom profile of bladder pain, urinary urgency, and increased urinary frequency is to be collectively termed as hypersensitive bladder symptoms.

Keywords Interstitial cystitis · Classification · Bladder pain syndrome · Hypersensitive bladder · Pathophysiology

Introduction

There is a group of patients who complain of pain related to the urinary bladder, often associated with persistent urge to void and increased urinary frequency all day. No remedies for infectious diseases or overactive bladder (OAB) do work. Imaging tests detect no significant abnormalities. Cystoscopy is apparently non-pathologic. The patients are frustrated because of no improvement despite of multiple clinical tests and endless treatment trials.

The patients may have an illness that has been called interstitial cystitis (IC). IC is characterized by pain symptoms related to the bladder with no specific clinical test results. The illness is also called painful bladder syndrome (PBS) [1], bladder pain syndrome (BPS) [2], interstitial cystitis/bladder pain syndrome (IC/BPS) [3], or hypersensitive bladder (HSB) [4]. Each nomenclature has its own rationale; meanwhile, the inconsistency of terminology hindered recognition of the disease. Consequently, the patients are less likely to have the correct diagnosis and proper management [5].

Recent studies, however, have elucidated the distinction of sub-groups of IC on the basis of histopathology and genetics. Clear classification and taxonomy are essential to make

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progress in clinical and basic research and provide effective treatments to the sufferers.

Current Classification

First, we need to understand the definition and difference of these resembling words.

Interstitial Cystitis

IC was first described in the nineteenth century and is currently alive as a medical term [6]. Despite its long history and popularity, there is no internationally agreed definition or diagnostic criteria of IC. The National Institute of Diabetes and Digestive and Kidney Diseases proposed the NIDDK criteria in 1996, which required symptoms and cystoscopic findings (Hunner lesions or glomerulations) with numerous exclusions [7]. The NIDDK criteria, however, were not the diagnostic standard but a requirement for the enrollment of clinical trials of IC patients. No definitions of IC are given in "Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis" by the European Society for the Study of Interstitial Cystitis or International Society for the Study of Bladder Pain Syndrome (ESSIC) [2] and "The Clinical Guideline for the Diagnosis and Treatment of Interstitial Cystitis/Bladder Pain Syndrome" by the American Urological Association (AUA) [3]. In addition, these guidelines use BPS or IC/BPS instead of IC to refer the illness. "Clinical guidelines for interstitial cystitis and hypersensitive bladder" published by East Asian urologists (East Asian guidelines) adapt IC, defining it as a bladder disease with non-specific inflammation and urinary urgency, frequency, and bladder pain [4]. However, a part of "IC" patients demonstrates fairly the normal bladder without inflammation.

The consensus would be that IC is a disorder of the urinary bladder of unidentified reasons; the patients have a symptom complex comprising of bladder pain, bladder discomfort, and urinary frequency; however, findings of cystoscopy and histopathology are variable.

Subtypes of Interstitial Cystitis

It has been recognized that the urinary bladder of some IC patients has Hunner lesions. The lesion is also called "Hunner's ulcer" or simply "ulcer." Histologically, it is not associated with defective sub-epithelial tissue thus not an ulcer but erosion, although. A Hunner lesion is observed on cystoscopy as a reddish mucosal lesion with covering clots and converging vessels or scars (Fig. 1).

It is also known that the urinary bladder of some IC patients undergoes bleeding after fully distending the urinary bladder under sufficient anesthesia (hydrodistension). This mucosal bleeding after distension (MBAD) is usually self-limiting, and the second-look cystoscopy finds post-MBAD spots in the bladder (glomerulations). These findings were believed to be a diagnostic criterion of IC, as documented in NIDDK criteria.

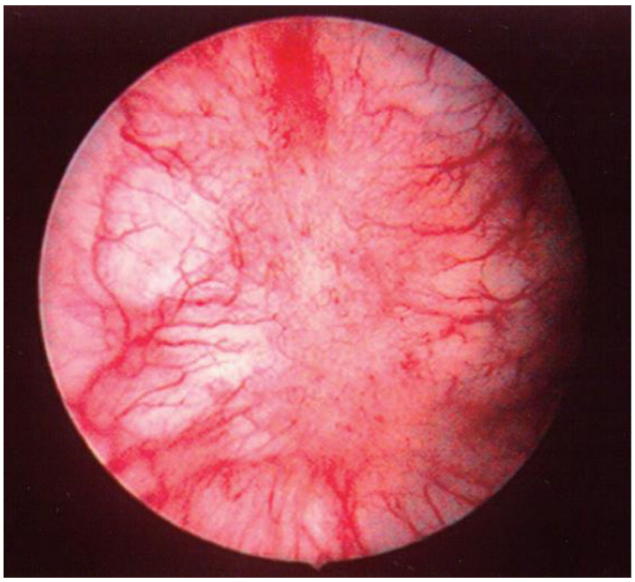

Fig. 1 A Hunner lesion of 69-year-old female. The lesion is a reddish and flat mucosal change accompanied by converging vessels

IC is sub-grouped by Hunner lesion and glomerulations. IC with Hunner lesions is called classic IC, ulcer-type IC, ulcerative IC, or Hunner type IC (HIC). IC without Hunner lesions is logically termed non-classic IC, non-ulcer-type IC, non-ulcerative IC, or non-Hunner type IC (NHIC). In reality, however, NHIC is restricted to IC without Hunner lesions but with glomerulations. It is not the word for patients lacking both Hunner lesions and glomerulations. This illogic terminology may come from a belief that IC patients should have some cystoscopic abnormalities. East Asian Guidelines and ESSIC Guidelines provide HSB [4] and BPS type 1 [2], respectively, for the patients lacking both Hunner lesions and glomerulations.

Painful Bladder Syndrome

PBS is mentioned in the 2002 terminology report by the International Continence Society (ICS) [1]. It says "suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and night-time frequency, in the absence of proven urinary infection or other obvious pathology." The report states that "PBS is a preferable term to IC, which is a specific diagnosis and requires confirmation by typical cystoscopic and histological features." Regrettably, there is no further explanation of the "typical" features of cystoscopy and histology. Nevertheless, this

statement indicates the authors' assumption that there are "typical" features of cystoscopy and histology for IC.

The ICS report also mentions "Syndromes describe constellations, or varying combinations of symptoms, but cannot be used for precise diagnosis. The syndromes described are functional abnormalities for which a precise cause has not been identified. It is presumed that routine assessment has excluded obvious local pathologies." It also proposes genitourinary pain syndrome and symptom syndromes suggestive of lower urinary tract dysfunction. The former further divided into PBS and pelvic pain syndrome, and the latter into overactive bladder syndrome and lower urinary tract symptoms suggestive of bladder outlet obstruction, respectively.

Bladder Pain Syndrome

BPS would be a replacement for PBS, since harmonization of the nomenclature of pain syndromes requires the organ name to come first. However, it is not a simple replacement but something more. ESSIC defines BPS as "chronic (lasting > 6 months) pelvic pain, pressure, or discomfort perceived to be related to the urinary bladder and accompanied by at least one other urinary symptom such as a persistent urge to void or increased frequency of urination" [2]. Confusable diseases must be excluded. ESSIC further divides BPS into type 1 (no Hunner lesions and no glomerulations), type 2 (no Hunner lesions but with glomerulations), and type 3 (with Hunner lesions). BPS is as an umbrella term covering all the symptomatic patients after confusable disease exclusion and also provides sub-classification based on cystoscopy. At the same time, however, BPS as an umbrella term gives an impression that the BPS patients of any types have common etiology despite different cystoscopic findings. IC is totally excluded from the BPS nomenclature system.

Interstitial Cystitis/Bladder Pain Syndrome

IC has a long history and is commonly used in both medical and general societies. The long history may have allowed multiple interpretations among users. IC can be interpreted as HIC (with Hunner lesions), HIC plus NHIC (with Hunner lesions or glomerulations as NIDDK criteria), HIC plus NHIC plus HSB (symptomatic patients after exclusion of confusable diseases regardless of cystoscopic findings), or even patients with mimicking symptoms "prior to" rigid exclusion of confusable diseases. The last interpretation is common in prevalence study of "IC." Coining a new word is thus preferable to promote scientific accuracy. However, abandoning IC (and replacing IC by BPS), as advocated by ESSIC, may be too hasty. A compromise would be a connecting word, IC/BPS.

IC/BPS is defined by AUA as an unpleasant sensation (pain, pressure, or discomfort) perceived to be related to the urinary bladder and associated with lower urinary tract symptoms lasting > 6 weeks in the absence of infection or other identifiable cause [3]. It looks fairly the same as BPS. The difference would be preserving IC (IC/BPS) or abolishing IC (BPS alone).

Hypersensitive Bladder

HSB is a concept proposed by East Asian Guidelines. It is defined by hypersensitive bladder symptoms (discomfort, pressure, or pain in the bladder usually associated with urinary frequency and nocturia) and no proven bladder pathology (no abnormal findings on cystoscopy) or other explainable diseases [4]. It corresponds to ESSIC BPS type 1; the patients are lacking both Hunner lesions and glomerulations. HSB is different from BPS type 1 in that its wording takes after overactive bladder (OAB). OAB is a functional disorder of the urinary bladder with specific symptoms such as urinary frequency, urinary urgency, and urgency incontinence. HSB is also a functional disorder of the urinary bladder with hypersensitive bladder symptoms. OAB and HSB may share frequency and urgency as the common symptoms, although pain is the hallmark symptom in HSB [8].

Differences Depending on Guidelines

Table 1 summarizes the classification/definition of IC-related terms of various clinical guidelines. Using Hunner lesions and glomerulations as the classification factor, three categories can be presumed. The AUA Guidelines use IC/BPS as a single term combining all presumed classifications without subgrouping. ESSIC uses BPS as the umbrella term and divides it into type 1, type 2, or type 3, depending on the presence or absence of Hunner lesions and/or glomerulations. The East Asian Guidelines have no umbrella term and give three categories: HIC, NHIC, and HSB according to the presence or absence of Hunner lesions and/or glomerulations.

Table 1 Classification of IC and IC-related conditions in different guidelines

Endoscopic findings			
Hunner lesions	+	−	
Glomerulations	+/−	+	−
Terminology			
AUA	IC/BPS		
ESSIC	BPS		
	Type 3	Type 2	Type 1
East Asia	HIC	NHIC	HSB

IC interstitial cystitis, *BPS* bladder pain syndrome, *HIC* Hunner type IC, *NHIC* non-Hunner type IC, *HSB* hypersensitive bladder

Hunner Lesions and Glomerulations

Hunner lesions and glomerulations are regarded as the critical classifiers of IC. Recent research progresses relevant to Hunner lesions and glomerulations are to be discussed below. For the sake of convenience, the terminology hereafter follows the East Asian Guidelines: HIC for the presence of Hunner lesions, NHIC for the absence of Hunner lesions and presence of glomerulations, and HSB for the absence of both Hunner lesions and glomerulations (Table 1) [4].

Hunner Lesions

A Hunner lesion would be the "typical" endoscopic feature of IC. NIDDK criteria regarded it as the definitive or automatic diagnostic finding of IC. However, many urologists, believing that the lesions are very rare, have never seen the lesions or never attempted to detect the lesions. The lesion is erroneously believed a hemorrhagic defective mucosa as is described as an ulcer. The scare experience and misbelief causes inconsistency in diagnostic criteria for the Hunner lesions, which is suggested by variable proportions of Hunner type IC despite a high performing rate of endoscopy [9].

Our experience indicates more than a half of IC patients carry Hunner lesions (Fig. 1). The lesion is a reddish and flat mucosal change, and not an ulcer. It is commonly located in the upper portion of the posterior wall but may exist anywhere in the bladder. The shape of lesions is mostly belt-like, is occasionally oval, and may be distorted by scars; the lesions are often accompanied by converging vasculatures and scars in the vicinity. They are sometimes covered by debris or blood clots. Close view of lesions shows tangled short micro-vessels and no normal capillary structure. A clinical trick is that the lesions quickly become invisible as the bladder is distended. Filling at a minimal volume for observation is important to avoid overlooking. The lesions easily bleed; a soft touch by the endoscope may cause bleeding. As the bladder is distended, the lesion can turn into crack or fissure, which undergoes massive and pulsatile bleeding on decompression of the bladder.

Histopathology of lesions is believed to be characterized by non-specific inflammation and/or dense mast cell infiltration. We routinely take cold cup biopsies from the lesions and apparently normal mucosa outside the lesions (non-lesion area or background mucosa). Histopathology of the HIC bladder tissue, regardless taken from the lesions or background mucosa, shows totally different features from NHIC [10••]. The HIC bladder demonstrates severe inflammation with lymphoplasmacytic cells, stromal edema, and increased vascularity, while the NHIC bladder was almost normal, with scattered lymphocytes and occasional stromal edema. Epithelial denudation is another characteristic feature of HIC, and the detachment is hardly seen in NHIC and non-IC chronic cystitis. The increased lymphocyte aggregation and epithelial denudation are confirmed by digital quantification using image analysis software. Important to note, these changes are observed not only in Hunner lesions but also in non-lesion background mucosa. In other words, HIC is histologically characterized by pan-cystitis and epithelial denudation.

Further studies exhibit B cell abnormality as another distinct feature of HIC bladder. The infiltrating B cells are biologically activated as demonstrated by co-localization of CXCR3 with CD138 [11•]. Light-chain restriction, the index of B cell clonal expansion, is frequently observed in the HIC bladder. The infiltrating lymphocytes are thus likely to recognize some antigens and produce specific antibodies, and this active immunological process should sustain persistent continuous inflammatory reactions in the bladder.

Gene expression studies have proved the overexpression of pro-inflammatory cytokines and ligands or cellular receptors to noxious stimuli including IL-10, IL-17A, iNOS, IL-12A, FGF7, CXCL1, CCL21, and TNF [12, 13•]. The HIC bladder is also characterized by antigen-mediated allergic inflammation and T cell-mediated immune responses [14, 15•, 16]. Most recently, the whole-transcriptome profiling indicates a clearly separated, distinct gene expression profiling of HIC from NHIC, HSB, and controls [17••]. Bladder tissue of HIC patients alone showed the overexpression of vascular endothelial growth factor (VEGF) and B cell activating factor (BAFF) at both the RNA and protein levels, and higher density of sub-epithelial microvasculature and inflammatory infiltrates. By contrast, these features did not differ significantly between NHIC and HSB and controls.

Glomerulations

Glomerulations are a diagnostic criterion for a specific type of IC (NHIC) in NIDDK criteria. However, a recent review article casts doubt on the diagnostic significance of this finding [18•]. The review found no consistent connection between glomerulations and the diagnosis or between the severity of symptoms and the number of glomerulations. Glomerulations are found in healthy asymptomatic populations as well as in symptomatic populations with other diseases. The grade of glomerulations may change with time. Hence, the authors of the review article concluded that there is no convincing evidence that glomerulations should be included in the diagnosis or phenotyping of IC.

The conclusion would be agreeable; however, glomerulations should not be dismissed simply as "meaningless." What is observed on cystoscopy is mucosal bleeding after hydrodistension (MBAD) during emptying phase. The bleeding is self-limiting, and the second-look cystoscopy finds post-MBAD spots in the bladder, which are called glomerulations. MBAD may be minimal and regional but occasionally mild and extensive. The extensive MBAD is so

impressive that we cannot believe it as a normal variant. We need to continue the research on MBAD for its biological backgrounds and possible relevance to IC symptoms.

A misunderstanding on glomerulations is "Bleeding from Hunner lesions is a kind of glomerulations." Certainly a Hunner lesion may undergo massive and arterial bleeding after overdistension. However, this bleeding is not MBAD. MBAD is a mild venous bleeding and takes place from mucosa that appears normal before distension. Another potential misunderstanding is "Bloody drainage after distension is indicative of glomerulations." Bleeding may come from Hunner lesions that have been overlooked on pre-distension cystoscopy. Cystoscopy throughout early filling, distension, and emptying phases is recommended to monitor the mucosal changes: Hunner lesions, crack of Hunner lesions, bleeding of Hunner lesions, and MBAD.

Requirement for Terminology

When revisiting the terminology related to IC, we need to consider three aspects. The first is pathophysiology supported by scientific evidence. The second is proper clinical management, and the third is adaptability to the society.

Underlining Pathophysiology

The most important classifier of a disease is pathophysiology. In this regard, HIC is a distinct inflammatory disorder characterized by specific genomic and histological features [19]. These changes are not observed in NHIC or HSB despite of similar symptoms. Therefore, the presence of Hunner lesions should be a crucial classification determinant.

Clinical Management

Recognition of Hunner lesions has significance in clinical management. The extent of lesions correlates with symptomatic severity and bladder capacity [20]. The lesion-targeted therapies such as electric or laser fulguration and intra-lesion injection of steroid are reported to provide long-lasting pain relief in HIC alone [21]. Administration of cyclosporine is also effective for HIC, probably by blocking activated immunoreactions [22, 23].

Regarding glomerulations, there is no convincing evidence that the finding should be included in the diagnosis or phenotyping of IC [18•]. From a practical point of view, hydrodistension is required to detect glomerulations and the procedure needs hospitalization and/or anesthesia. The degree of glomerulations is difficult to quantitate. Considering their diagnostic validity, cost, and reliability, glomerulations may be of least clinical significance as a classification determinant.

Despite variable cystoscopic findings, symptomatic presentations heavily overlap and are practically indistinguishable among HIC, NHIC, and HSB [24, 25]. A collective term for the symptom complex is preferable for convenience. An example is hypersensitive bladder symptoms. Hypersensitive bladder symptoms are compatible with biological evidence such as sensory hyperinnervation observed in HIC and NHIC but not in OAB [26] and increased expression of TRP family molecules and nerve growth factor in HIC and NHIC but not in controls [27].

Consistency with Social and Insurance Systems

Medical care is a social service usually supported by insurance system. The nomenclature of IC and its related conditions needs to fit in with the insurance language. IC is incorporated in the International Classification of Diseases (ICD) versions 10 and 11 (https://icd.who.int/). Insurance systems in many countries or regions reimburse medical care for IC but not for BPS or HSB. To comply with the current social system, the term IC should be retained in the classification.

Classification Proposed

Taken together, a taxonomy/classification is proposed (Table 2). It has an umbrella term, IC/BPS, and two subgroups, HIC (IC/BPS with Hunner lesions) and BPS (IC/BPS without Hunner lesions). The umbrella term is IC/BPS rather than BPS, because BPS is a symptom syndrome by functional abnormality and cannot be the upper-class category of HIC, a distinct inflammatory disorder with obvious local pathology. The common symptom complex is to be termed hypersensitive bladder symptoms.

The sub-group with Hunner lesions may be named IC/BPS with Hunner lesions, BPS type 3, HIC, or IC. Among these candidates, HIC most simply and explicitly expresses the presence of Hunner lesions. IC has multiple interpretations and may be misunderstood as HIC plus NHIC, for example. The sub-group without Hunner lesions is collectively to be called BPS without further division of the presence of glomerulations.

Table 2 Proposed classification of IC and IC-related conditions

Endoscopic findings			
Hunner lesions	+	–	
Glomerulations	+/–	+	–
Terminology			
Proposal	IC/BPS		
	HIC	BPS	

Future Perspectives

As mentioned above, HIC is a bladder disease with obvious organic changes while BPS is a dysfunctional condition like OAB. HIC and BPS share frequency/pain symptoms but have totally different etiology. In the future, IC/BPS will be disused; IC (HIC) may stand alone as a distinct disease, BPS and OAB being classified under an umbrella term such as functional bladder disorder.

Conclusions

A meaningful classification of IC and IC-related conditions such as BPS is mandatory for clinical and scientific progress. Patients with Hunner lesions differ in terms of histopathology, gene expression, and clinical management. The proposed classification/taxonomy comprises an umbrella term (IC/BPS) and two sub-groups, HIC (IC/BPS with Hunner lesions) and BPS (IC/BPS without Hunner lesions). IC/BPS, a collective term for symptomatic patients, is convenient for initial management. HIC, a sub-group of IC/BPS with Hunner lesions, is useful for the specific management. The common symptomatic profile is termed as hypersensitive bladder symptoms.

Compliance with Ethical Standards

Conflict of Interest Yukio Homma has received speaker honorarium from Astellas, Nippon Chemiphar, and Pfizer, outside the submitted work.

Yasuhiko Igawa has received grants from Kissei, Kyorin, RaQualia, Nippon-Shinyaku, Astellas, Lilium Otuka, Takeda, Tsukada Research Medical, Integral, and Medicon, outside the submitted work. Yasuhiko Igawa has received speaker honorarium from Kissei, Kyorin, Nippon-Shinyaku, Astellas, outside the submitted work.

Yoshiyuki Akiyama, Aya Niimi, and Akira Nomiya declare that they have no conflict interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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