BJU International (2000), **85**, 995–999

Interstitial cystitis: a review of immunological aspects of the aetiology and pathogenesis, with a hypothesis

J.P. VAN DE MERWE and H.J. ARENDSEN*

*Department of Immunology and Internal Medicine III, University Hospital and Erasmus University Rotterdam, Rotterdam, and *Department of Urology, Diaconessen Hospital, Leiden, The Netherlands*

Introduction

Inflammation of the bladder is a common disease mainly affecting women. Patients may complain of suprapubic pain, urinary frequency and urgency with or without haematuria on repeated occasions. In many cases, urine analysis reveals white and red blood cells, while a positive bacteriological culture will confirm an infectious cause of the cystitis. However, if the culture is negative, with or without cells, interstitial cystitis (IC) should be suspected. IC is a poorly understood syndrome that, like bacterial cystitis, occurs primarily in women. Lack of awareness of IC by the physician or the use of an inappropriate diagnostic approach may result in a lengthy period for many patients between the onset of symptoms and diagnosis of IC.

IC is a chronic inflammatory bladder disorder of unknown aetiology. Bladder histology, showing infiltrates of mast cells, eosinophilic leukocytes and T lymphocytes, suggests that the disease is mediated by the immune system. The clinical association of IC with thyroid disorders and systemic autoimmune diseases such as systemic lupus erythematosus [1] and Sjögren's syndrome [2], has led to the hypothesis that IC may be an autoimmune disease of the bladder. However, the triggering factor that leads to disease is still unknown, as is the case with the associated autoimmune diseases. The most prevalent aetiological theories of IC are:

- Increased permeability of the bladder epithelium, caused by deficient glycoproteins and glycosaminoglycans (GAGs) of the glycocalyx, allowing urine components to damage the bladder wall.
- Mast cell activation and degranulation by specific (IgE binding) or nonspecific (e.g. drugs, hormones, acetylcholine) stimuli, leading to the release of pre-stored (e.g. histamine, heparin, tryptase) or *de novo* produced (e.g. leukotrienes, PGs, thromboxanes) mediators of inflammation.
- Infiltration of the bladder wall, induced by unknown stimuli, with lymphocytes, plasma cells, neutrophilic and eosinophilic granulocytes, and mast cells (= inflammation).
- Toxic urine components
- Occult infection
- Increased nerve fibre density

However, none of these factors is sufficiently substantiated by experimental or clinical evidence.

In this review we present published immunological data on the aetiology and pathogenesis, and a novel hypothesis of how IC may be caused, based on our recent finding of an association between IC and Sjögren's syndrome.

Definition

There is no clear definition of IC as the clinical symptoms and histology are not specific. The diagnosis is essentially a syndrome diagnosis that can only be based on the combination of chronic irritative voiding symptoms, sterile and cytologically negative urine, characteristic cystoscopic findings and the exclusion of other diseases [3]. The diagnosis of IC requires a thorough patient history, cystoscopy carried out under anaesthesia with hydrodistension of the bladder and deep bladder biopsies.

IC primarily occurs in women (80–85%) and typical symptoms consist of urinary frequency, urgency, nocturia and pain in the lower abdominal region. The pain is often associated with bladder filling and relieved by urination. Many patients have periods of remission and exacerbation, and the condition is chronic. Symptoms may worsen perimenstrually in about half of the affected women. Cystoscopically, IC is characterized by petechial bladder mucosal haemorrhages ('glomerulations'). Severe IC is associated with reduced bladder capacity and in rare cases with the classic Hunner's ulcer.

There is no consensus about the need for a bladder biopsy for the diagnosis of IC. However, in recent years deep bladder biopsies have been considered essential for

the diagnosis as they exclude other bladder diseases, e.g. carcinoma and tuberculosis, while confirming the histological abnormalities of IC.

Epidemiology

It is not surprising that it is difficult to reliably assess the prevalence and incidence of a disease for which the diagnosis is not firmly defined. There are consequently few published epidemiological studies and the results are variable. In a Finnish study the prevalence was 18.1 per 100 000 in women and 10.6 per 100 000 in the whole population, with an annual incidence of 1.2 cases per 100 000 [4]. In the Netherlands, Bade *et al.* [5] calculated a prevalence of 8–16 cases in 100 000 women. A recent study in the USA showed a much higher prevalence of 52–67 cases per 100 000 women [6].

Pathology

On the basis of cystoscopic appearance, two types of IC are generally recognized: the classic ulcerated type and the early un-ulcerated type. Johansson and Fall analysed 210 patients, 146 with an ulcer type and 64 with no ulcers; the mean age of the ulcer group was 57 years and of the second group 38 years, suggesting that the latter type may be an early manifestation of IC [7].

The pathology of the second type showed suburothelial haemorrhages corresponding to glomerulations in 90% of the patients, while mucosal ruptures were seen in 83%. Overall, most showed only mild inflammatory changes, but oedema and dilated vessels were frequently seen.

In the ulcer type, inflammatory changes were limited to the lamina propria in $\approx 90\%$ of the patients. Significant detrusor muscle fibrosis was seen in only 10% of the patients. Ulcerations were usually wedge-shaped, extended down to the lamina propria and were generally not deeper than the level of the muscularis mucosae. The urothelium was either absent or floating above the surface.

The inflammatory infiltrate seen in IC is predominantly composed of T lymphocytes, with more plasma cells as the degree of inflammation increases [8–10]. Submucosal inflammation is associated with denuded epithelium, ulceration and pyuria. Epithelial and basement membrane thickness, submucosal oedema, vascular ectasia, fibrosis, and detrusor muscle inflammation and fibrosis may also occur but are not specific for IC [11]. An increase has been found in the numbers of macrophages, activated lymphocytes and vascular endothelial cells expressing HLA class II molecules within the submucosa [12].

The diagnostic value of mast cell counts is a subject of controversy. Larsen *et al.* [13] found a highly significant increase in the number of mast cells within the detrusor muscle bundles in patients with IC. Lynes *et al.* [14] found a strong relationship between detrusor mast cell density, especially degranulated, and the degree of epithelial loss, submucosal inflammation, epithelial ulceration, urinary pyuria and response to treatment. However, recent studies indicated that mast cell counts are not useful in the evaluation of IC and do not allow inclusion or exclusion of a diagnosis of IC. Furthermore, an ultrastructural analysis of all tissue components did not support a primary pathogenetic role of mast cells or a selectively deficient GAG layer [15,16]

Epithelial cells of lesional and uninvolved bladder tissue usually stain positively for IgA, which may be focal or may diffusely involve all layers of the epithelium. Staining for IgE correlates with the presence of mast cells and is seen in $< 2\%$ of cases, also suggesting that mast cells have no prominent role in the pathogenesis of the disease. Eosinophil density in bladder biopsies was uniformly low and similar in IC and control patients. Lynes *et al.* [14] found no evidence of a relationship between the eosinophil and the inflammatory process of IC.

Electron microscopy shows a widening of the interstitium between urothelial cells [17]. Elbadawi and Light [16] found a distinctive combination of peculiar muscle cell profiles, injury of intrinsic vessels and nerves in the muscularis and suburothelium. A dis-cohesive urothelium was observed in lesional and less markedly in non-lesional bladder samples. Marked oedema of various tissue elements and cells appeared to be common. Urothelial changes disrupted the permeability barrier. Vascular lesions included endothelial cell injury and suggested a slow microcirculation. Neural changes included a combination of degenerative and regenerative features.

It can be concluded from these data that the pathological findings in IC indicate no specific causal mechanism, but mainly reflect the chronic inflammatory nature of the disease.

Aetiology and pathogenesis

Aetiology

The aetiology of IC is unknown and, as in other diseases with no known cause, many theories have been published. IC has been suggested to be of an autoimmune, allergic, infectious, neurological, vascular or mechanical nature, or caused by infiltration and damage of the bladder wall by activated mast cells, and/or an altered bladder lining permitting entry of allergenic or toxic substances into the underlying tissues [18,19]. Using an rDNA bacterial PCR to study bladder biopsies and sterile urine samples from patients with IC, Haarala *et al.* [20] excluded an ongoing bacterial infection as the cause of IC.

The role of mast cells in the bladder wall of IC is highly controversial. The increase in the number of mast cells is not specific for IC as it occurs in many other (chronic) bladder diseases. Ultrastructural studies also failed to support a primary pathogenetic role of mast cells, but a leaky urothelium and mast cell activation may be a result of a self-perpetuating process of neurogenic inflammation [16].

IC is not an organ-specific disease as many patients have systemic symptoms and blood abnormalities (see below), suggesting that IC may be a local expression of a generalized disease. The association of IC with systemic lupus erythematosus has been known for a long time, with a 30-fold increased risk, and this magnitude of increased risk was also found with Sjögren's syndrome [2]. Furthermore, a recent study revealed a 100-fold increase of inflammatory bowel disease (Crohn's disease and ulcerative colitis) in patients with IC [21]. The arguments in favour of an autoimmune nature of IC are:

- IC occurs more frequently in women than in men
- no microorganism or other cause has been found in IC
- IC is frequently associated with arthritis, systemic lupus erythematosus, thyroid disorders and Sjögren's syndrome
- IC is often accompanied by joint pain, muscle pain, fatigue, intestinal disorders and medicine intolerance
- blood tests often show abnormalities such as increased IgG, decreased C4, antinuclear antibodies (ANA) and antibodies to mitochondria and parietal cells
- mainly CD4 + T lymphocytes are found in the inflamed bladder wall of patients with IC.

Pathogenesis

Several studies have shown abnormalities in IC that may play a role in the pathogenesis of the disease. A small peptide that inhibits the proliferation of normal bladder epithelial cells *in vitro* has been detected in the urine of 86% of patients with IC, in 12% of women with bacterial cystitis and in 8% of normal control subjects [22]. This antiproliferative factor was subsequently found to originate from the distal ureter or urinary bladder [23]. The factor needs to be identified to fully understand its relevance and origin in IC.

Diffusion of urinary potassium into the bladder interstitium induces sensory symptoms and damages tissue in IC [24]. This may be important in patients with coexisting Sjögren's syndrome, as distal renal tubular acidosis with increased urinary potassium excretion is common in the latter disease.

Bade *et al.* [25] showed the presence of IgG autoantibodies against bladder epithelium and muscle fibres in all of three patients with IC who were tested.

The chronic lymphocytic infiltrate probably causes bladder fibrosis as this relationship is also seen in other diseases, e.g. Crohn's disease and sarcoidosis.

Immunology

Blood abnormalities

Sera from patients with IC showed significant depletion of complement C4 and markedly elevated IgG levels [26], suggesting activation of the classic complement pathway by (auto)antibodies. Studies on peripheral blood lymphocyte subsets showed increased numbers of B lymphocytes and activated lymphocytes [2,27], or were found to be entirely normal [8]. Antinuclear antibodies (ANA) at titres of $\geqslant 1:40$ have been found in 36–60% of patients with IC [2,28]. However, these abnormalities are not specific and are seen in other chronic inflammatory diseases with immunologically mediated tissue damage.

Urine abnormalities

Thirty-three urine specimens from 14 patients with IC showed acute inflammation, predominantly polymorphonuclear cells; 14 (42%) specimens contained eosinophils and 10 (30%) contained cells resembling mast cells. Other findings included numerous degenerated cells, reactive transitional cells and haematuria [29]. Levels of tryptase, a mast cell-derived enzyme in 24 h urine samples, but not in 'spot' urine samples, are much higher in patients with IC [19].

Systemic clinical features

Van de Merwe *et al.* [2] investigated 10 patients with IC for the presence of systemic autoimmune diseases, in particular for Sjögren's syndrome, which is diagnosed on the basis of coexisting involvement of lachrymal and salivary glands, leading to keratoconjunctivitis sicca (KCS) and focal lymphocytic sialadenitis (FLS), respectively. Other features consist of arthralgia and disabling fatigue in 80% of the patients. Serological abnormalities include antinuclear antibodies, rheumatoid factors and antibodies to SS-A/Ro and SS-B/La. In two patients both KCS and FLS were present, thus diagnosing Sjögren's syndrome. Additionally, in six patients one of these two features was present; KCS in three and FLS in three. Unpublished data (van de Merwe, Arendsen and Hooijkaas) of a preliminary analysis of 80 patients with IC showed that 14% also had Sjögren's syndrome, 26% KCS and 5% FLS.

Alagiri *et al.* [21] conducted a questionnaire-based

study evaluating 12 disease processes and surveying the characteristics of IC in a population of 2405 individuals with IC who responded to the initial survey; an additional 277 individuals were randomly selected and individually contacted. Compared with the general population, individuals with IC were 100 times more likely to have inflammatory bowel disease (7.3%, population 0.07%) and 30–50 times more likely to have systemic lupus erythematosus (1.7%, population 0.05%). In addition, there were increased frequencies of allergies (40.6%; population 22.5%), irritable bowel syndrome (25.4%, population 2.9%), sensitive skin (22.6%, population 10.6%), and fibromyalgia (12.8%, population 3.2%) [21,30] in patients with IC.

Hypothesis

If it is true that IC, systemic lupus erythematosus and Sjögren's syndrome are all expressions of a comparable disturbed immunological mechanism, recent and intriguing findings in Sjögren's syndrome may be relevant for IC. Sjögren's syndrome is an autoimmune exocrinopathy with general mucosal dryness and systemic symptoms. Histologically it is characterized by periductal focal infiltration of exocrine glands with mainly T lymphocytes. In patients and animal models the infiltration of exocrine glands does not fully explain the lack of secretory function of the glands. Additionally, autoantibodies to the acetylcholine receptors, e.g. the muscarinic M_3-receptors, in salivary and lachrymal glands can functionally block these receptors [31,32]. This can partly be overcome by muscarinic agonists such as pilocarpine hydrochloride [33,34]. Autoantibodies to the muscarinic M_1-receptor have also been detected in patients with Sjögren's syndrome [35]. Myasthenia gravis, an autoimmune disease also associated with Sjögren's syndrome and systemic lupus erythematosus, is mediated by autoantibodies to the nicotinic acetylcholine receptor at the surface of striated muscles [36].

Studies on Graves' disease have clearly shown that antibodies to the thyroid-stimulating hormone receptor may stimulate or block receptor functions, or even show alternating stimulation and blocking in time within the same patients [37].

The human detrusor smooth muscle is endowed with muscarinic M_1-, M_2-, and M_3-receptors, with direct and indirect effects on smooth muscle contraction [38,39]. Furthermore, carbachol, a muscarinic receptor agonist, has been found to trigger serotonin release from rat bladder mast cells in a dose-dependent manner, an effect increased by pre-treating tissue with oestradiol, and that is blocked by atropine [40]. Recently, IgG autoantibodies against epithelium and muscle fibres were found in patients with IC [25].

Stimulating and/or blocking autoantibodies to various subtypes of muscarinic receptors could theoretically be responsible for both exocrine dysfunction and detrusor smooth muscle contractions. It is well known that antibodies can attract inflammatory cells to the sites of their antigen binding as a consequence of the activation of complement proteins, with the release of chemotactic fragments. The observation that inflammatory infiltrates are mainly seen in late stages of the disease [7] is in line with this hypothesis.

Summary

IC is a complex syndrome consisting of urinary voiding symptoms, lower abdominal pain and signs of chronic inflammation at cystoscopy and pathology. The cause of the disease is unknown but the infiltration of the bladder wall by mainly T lymphocytes in addition to mast cells, the occurrence of autoantibodies in many patients and the association with systemic autoimmune diseases suggest an autoimmune nature of the disease.

The strong association of IC with Sjögren's syndrome warrants the exploration of comparable mechanisms in both diseases. Recent data on Sjögren's syndrome suggest that initial abnormalities may consist of autoantibodies to the muscarinic M_3- receptors, causing impaired nervous stimulation of the exocrine glands. Inflammatory changes may be a late consequence of the binding of these autoantibodies to the receptors. It is postulated that autoantibodies to various subtypes of muscarinic receptors on detrusor smooth muscle could theoretically explain initial voiding symptoms and late inflammatory changes in the bladder in IC and the association of IC with Sjögren's syndrome.

Acknowledgements

The authors thank Jane Meijlink for her grammatical help.

References

1 Orth RW, Weisman MH, Cohen AH, Talner LB, Nachtsheim D, Zvaifler NJ. Lupus cystitis: primary bladder manifestations of systemic lupus erythematosus. *Ann Intern Med* 1983; **98**: 323–6
2 Van de Merwe J, Kamerling R, Arendsen E, Mulder D, Hooijkaas H. Sjögren's syndrome in patients with interstitial cystitis. *J Rheumatol* 1993; **20**: 962–6
3 Messing EM. The diagnosis of interstitial cystitis. *Urology* 1987; **29**: 4–7
4 Oravisto KJ. Epidemiology of interstitial cystitis. *Ann Chir Gynaecol Fenn* 1975; **64**: 75–7
5 Bade JJ, Rijcken B, Mensink HJ. Interstitial cystitis in The Netherlands: prevalence, diagnostic criteria and therapeutic preferences. *J Urol* 1995; **154**: 2035–7
6 Curhan GC, Speizer FE, Hunter DJ, Curhan SG, Stampfer MJ.

Epidemiology of interstitial cystitis: a population based study. *J Urol* 1999; **161**: 549–52
7 Johansson SL, Fall M. Pathology of interstitial cystitis. *Urol Clin North Am* 1994; **21**: 55–62
8 MacDermott JP, Miller CH, Levy N, Stone AR. Cellular immunity in interstitial cystitis. *J Urol* 1991; **145**: 274–8
9 Christmas TJ. Lymphocyte sub-populations in the bladder wall in normal bladder, bacterial cystitis and interstitial cystitis. *Br J Urol* 1994; **73**: 508–15
10 Erickson DR, Belchis DA, Dabbs DJ. Inflammatory cell types and clinical features of interstitial cystitis. *J Urol* 1997; **158**: 790–3
11 Lynes WL, Flynn SD, Shortliffe LD, Stamey TA. The histology of interstitial cystitis. *Am J Surg Pathol* 1990; **14**: 969–76
12 Christmas TJ, Bottazzo GF. Abnormal urothelial HLA-DR expression in interstitial cystitis. *Clin Exp Immunol* 1992; **87**: 450–4
13 Larsen S, Thompson SA, Hald T *et al.* Mast cells in interstitial cystitis. *Br J Urol* 1982; **54**: 283–6
14 Lynes WL, Flynn SD, Shortliffe LD *et al.* Mast cell involvement in interstitial cystitis. *J Urol* 1987; **138**: 746–52
15 Dundore PA, Schwartz AM, Semerjian H. Mast cell counts are not useful in the diagnosis of nonulcerative interstitial cystitis. *J Urol* 1996; **155**: 885–7
16 Elbadawi AE, Light JK. Distinctive ultrastructural pathology of nonulcerative interstitial cystitis: new observations and their potential significance in pathogenesis. *Urol Int* 1996; **56**: 137–62
17 Said JW, Van de Velde R, Gillespie L. Immunopathology of interstitial cystitis. *Mod Pathol* 1989; **2**: 593–602
18 Theoharides TC, Sant GR, El-Mansoury M, Letourneau R, Ucci Aa Jr, Meares Em Jr. Activation of bladder mast cells in interstitial cystitis: a light and electron microscopic study. *J Urol* 1995; **153**: 629–36
19 Boucher W, El-Mansoury M, Pang X, Sant GR, Theoharides TC. Elevated mast cell tryptase in the urine of patients with interstitial cystitis. *Br J Urol* 1995; **76**: 94–100
20 Haarala M, Jalava J, Laato M, Kiilholma P, Nurmi M, Alanen A. Absence of bacterial DNA in the bladder of patients with interstitial cystitis. *J Urol* 1996; **156**: 1843–5
21 Alagiri M, Chottiner S, Ratner V, Slade D, Hanno PM. Interstitial cystitis: unexplained associations with other chronic disease and pain syndromes. *Urology* 1997; **49**: 52–7
22 Keay S, Zhang CO, Hise MK *et al.* A diagnostic in vitro urine assay for interstitial cystitis. *Urology* 1998; **52**: 974–8
23 Keay S, Warren JW, Zhang CO, Tu LM, Gordon DA, Whitmore KE. Antiproliferative activity is present in bladder but not renal pelvic urine from interstitial cystitis patients. *J Urol* 1999; **162**: 1487–9
24 Parsons CL, Greenberger M, Gabal L, Bidair M, Barme G. The role of urinary potassium in the pathogenesis and diagnosis of interstitial cystitis. *J Urol* 1998; **159**: 1862–6
25 Bade JJ. Interstitial cystitis: new clinical aspects. PhD Thesis Groningen State University 1996
26 Mattila J, Harmoinen A, Hallstrom O. Serum immunoglobulin and complement alterations in interstitial cystitis. *Eur Urol* 1983; **9**: 350–2
27 Harrington DS, Fall M, Johansson SL. Interstitial cystitis: bladder mucosa lymphocyte immunophenotyping and peripheral blood flow cytometry analysis. *J Urol* 1990; **144**: 868–71
28 Ochs RL, Stein TW Jr, Peebles CL, Gittes RF, Tan EM. Autoantibodies in interstitial cystitis. *J Urol* 1994; **151**: 587–92
29 Dodd LG, Tello J. Cytologic examination of urine from patients with interstitial cystitis. *Acta Cytol* 1998; **42**: 923–7
30 Clauw DJ, Schmidt M, Radulovic D, Singer A, Katz P, Bresette J. The relationship between fibromyalgia and interstitial cystitis. *J Psychiatr Res* 1997; **31**: 125–31
31 Robinson CP, Brayer J, Yamachika S *et al.* Transfer of human serum IgG to nonobese diabetic Igmu null mice reveals a role for autoantibodies in the loss of secretory function of exocrine tissues in Sjogren's syndrome. *Proc Natl Acad Sci USA* 1998; **95**: 7538–43
32 Bacman S, Perez Leiros C, Sterin-Borda L, Hubscher O, Arana R, Borda E. Autoantibodies against lacrimal gland M3 muscarinic acetylcholine receptors in patients with primary Sjogren's syndrome. *Invest Ophthalmol Vis Sci* 1998; **39**: 151–6
33 Vivino FB, Al-Hashimi I, Khan Z *et al.* Pilocarpine tablets for the treatment of dry mouth and dry eye symptoms in patients with Sjogren syndrome: a randomized, placebo-controlled, fixed-dose, multicenter trial. P92–01 Study Group. *Arch Intern Med* 1999; **159**: 174–81
34 Rhodus NL. Oral pilocarpine HCl stimulates labial (minor) salivary gland flow in patients with Sjogren's syndrome. *Oral Dis* 1997; **3**: 93–8
35 Borda E, Leiros CP, Bacman S, Berra A, Sterin-Borda L. Sjogren autoantibodies modify neonatal cardiac function via M1 muscarinic acetylcholine receptor activation. *Int J Cardiol* 1999; **70**: 23–32
36 Siden A, Lindahl G. Signs of Sjogren's syndrome in a patient with myasthenia gravis. *Acta Neurol Scand* 1990; **81**: 179–80
37 Kasagi K, Takeda K, Goshi K *et al.* Presence of both stimulating and blocking types of TSH-receptor antibodies in sera from three patients with primary hypothyroidism. *Clin Endocrinol* 1990; **32**: 253–60
38 Harriss DR, Marsh KA, Birmingham AT, Hill SJ. Expression of muscarinic M3-receptors coupled to inositol phospholipid hydrolysis in human detrusor cultured smooth muscle cells. *J Urol* 1995; **154**: 1241–5
39 Hegde SS, Eglen RM. Muscarinic receptor subtypes modulating smooth muscle contractility in the urinary bladder. *Life Sci* 1999; **64**: 419–28
40 Spanos C, el-Mansoury M, Letourneau R *et al.* Carbachol-induced bladder mast cell activation: augmentation by estradiol and implications for interstitial cystitis. *Urology* 1996; **48**: 809–16

Authors

J.P. van de Merwe, PhD, MD, Internist-Immunologist.
H.J. Arendsen, MD, Head of Clinical Immunology Unit.
Correspondence: Dr J.P. van de Merwe, Rotterdam University Hospital, Department of Immunology, EE828, PO Box 2040, 3000 CA Rotterdam, The Netherlands.
e-mail: vandemerwe@immu.fgg.eur.nl