Interstitial Cystitis and Sjögren’s Syndrome

Key words: interstitial cystitis, Sjögren’s syndrome, organ-specific disease, progression, immunosuppressive therapy

An interesting and rare case of interstitial cystitis associated with Sjögren’s syndrome (SS) is presented in this issue (1).

See also p 248.

Interstitial cystitis is a chronic inflammatory disease of the bladder of unknown etiology occurring mainly in women (90%), primarily during middle age (2). It is characterized symptomatically by suprapubic, pelvic, urethral, vaginal, and/or perineal pain on bladder filling, urgency, and frequent urination due to small capacity bladder. This pain is relieved by emptying of the bladder. The clinical diagnosis is supported by cystoscopic findings of focal glomerulations or ulcers (Hunner’s ulcer) in the bladder wall (3, 4, Table 1).

SS is a chronic organ-specific autoimmune disease characterized by lymphocytic infiltration of the salivary and lacrimal glands, resulting in keratoconjunctivitis sicca and xerostomia. However, half of the SS patients develop systemic disorders associated with various autoantibodies, especially anti-Ro/SS-A and anti-La/SS-B antibodies (5). During the progression of SS, lymphocytes infiltrate many organs. Systemic disorders associated with SS include those of the pulmonary, hepatic, renal, hematologic, and dermatologic, and various other systems. Interestingly, the organ involved is different in each individual, suggesting that organ selectivity is one of the outstanding characteristics of SS. Intestinal cystitis was recently observed in several patients with SS (1, 6–8), indicating that bladder involvement may also be associated with SS.

Interstitial cystitis demonstrates some of the characteristics of an autoimmune disease, including the presence of autoantibodies, chronic inflammation, episodic waxing and waning of the disease, and, in some cases, its resolution by steroid therapy (1, 7). Histologically, lymphocytic infiltration of the bladder of patients with interstitial cystitis has been observed (9). These infiltrates consist of B cell nodules, including germinal centers, plasma cells and dense sheets of T cells (9). Increased numbers of mast cells and deposits of immunoglobulin and complement have been reported in these patients (10–13), and autoantibodies have been detected in patients with interstitial cystitis (14–16). This disease possesses many of the clinical and pathological features of autoimmune diseases, suggesting that interstitial cystitis may be a chronic condition of the bladder involving an autoimmune response. In this regard, immunization of mice with a syngeneic bladder homogenate was shown to induce an experimental autoimmune cystitis in mice very similar to the human disease, and adoptive transfer of splenic cells was found to induce the disease in non-immunized, syngeneic mice (17).

Interstitial cystitis is associated with several known autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus (SLE) and Hashimoto’s thyroiditis (15, 18, 19). Bladder involvement in SLE has been described in several patients (20, 21), as well as cystitis, in which the urinary bladder wall contained deposits of IgG, IgM, IgA and complement (22). This condition, called lupus cystitis, suggested that bladder involvement may be a primary manifestation of SLE (23). The occurrence, severity and nature of lower urinary tract symptoms, especially irritable bladder symptoms, was shown to be greater among patients suffering from SS or SLE than among age- and sex-matched controls (8). In an examination of 10 interstitial cystitis patients for the presence of systemic autoimmune diseases, it was found that two of these patients fulfilled the classification criteria for SS, while 3 other patients showed positive results on lip biopsy, indicating an association between interstitial cystitis and SS (6).

Although the etiology of SS and its mechanism of progression are not known, two factors may be important for understanding this complex disorder. The first is the microenvironment of the organ, which facilitates the migration of specific lymphocytes from the blood stream. The second is the continuity of lymphocyte aggression, which is probably mediated by antigen stimulation and dysregulation of apoptosis. The organ specificity observed in SS may be caused by homing of lymphocytes to specific organs that express adhesion molecules such as MadCAM-1 or E-selectin on their vessel walls or epithelial cells (24). The latter may be due to activation of the cells by viral infection (25) or another, as yet unknown, mechanism of activation. The homing of lymphocytes expressing α4β7 or αEβ7 may be facilitated by the expression of MadCAM-1 or E-selectin on the vessel wall. In SS, the aberrant expression of class II molecules in conjunction with autoantigens such as Ro/SS-A (26) or α-fodrin (27) and costimulating molecules such as B7.1 and B7.2 (28), on the surface of stimulated ductal cells may be the important step in the initiation and self-perpetuation of the local autoimmune reaction in various organs.
Table 1. Consensus Criteria for Diagnosis of Interstitial Cystitis (37)

<table>
<thead>
<tr>
<th>Automatic Exclusions</th>
<th>Positive Factors</th>
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<tr>
<td>Less than 18 years old</td>
<td>Pain on bladder filling relieved by emptying</td>
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<tr>
<td>Benign or malignant bladder tumors</td>
<td>Pain (suprapubic, urethral, vaginal, or perineal)</td>
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<tr>
<td>Radiation cystitis</td>
<td>Glomerulations after hydrodistention on cystoscopy</td>
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<tr>
<td>Bacterial cystitis</td>
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<td>Vaginitis</td>
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<td>Cyclophosphamide cystitis</td>
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<tr>
<td>Symptomatic urethral diverticulum</td>
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<tr>
<td>Uterine, cervical, vaginal, or urethral cancers</td>
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<tr>
<td>Active herpes</td>
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<td>Bladder or lower urethral calculi</td>
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<td>Waking frequency less than five times in 12 h</td>
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<td>Nocturia less than twice nightly</td>
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<td>Symptoms relieved by antibiotics, urinary antiseptics, urinary analgesics (e.g., phenazopyridine hydrochloride)</td>
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<td>Duration less than 12 months</td>
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<tr>
<td>Involuntary bladder contractions (urodynamics)</td>
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<td>Capacity greater than 400 ml, absence of sensory urgency</td>
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Endothelial overgrowth and intraepithelial lymphocytic infiltration, especially with dense infiltration of lymphocytes in the submucosal area, have been observed in the bladder of patients with autoimmune diseases (1, 9, 29, 30), suggesting that autoimmune epithelitis (31) may contribute substantially to the pathophysiology of organ involvement in SS. During this process organ-specific autoantigens may be expressed by apoptotic cells (27, 32). Continuous stimulation by autoantigens can activate T cells, leading to the expression of CD40L on the cell surface. The binding of CD40L on T cells to CD40 on B cells is a critical component of B cell stimulation. In addition, overexpression of Bcl-2, in the absence of chromosomal translocation, may occur during this T cell-B cell interaction, resulting in inhibition of apoptosis of B cells. Increased secretion by lymphocytes of cytokines such as IFN-γ, IL-2, IL-4, IL-5, IL-6, IL-10 and IL-13, along with increased secretion by epithelial cells of cytokines such as TNF-α, IL-1, IL-6 and IFN-γ and of chemokines such as IP-10 and MIG, are facilitating factors in the suppression of apoptosis and the proliferation of T and B lymphocytes (33, 34).

Although corticosteroid therapy is usually ineffective in the treatment of lupus cystitis and consequent obstructive uropathy (35, 36), combination therapy with prednisolone and cyclosporine has been found to be effective, even in cases of dryness associated with SS (1). It is worthwhile to consider this therapy in the future treatment of patients with SS with various organ involvement.

References


