The combination therapy of prednisolone and tacrolimus for severe painful bladder syndrome/interstitial cystitis

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Abstract

A 47-year-old woman visited our hospital with complaints of frequent urination and intensive pelvic pain. Painful bladder syndrome/interstitial cystitis (PBS/IC) was suspected based on her symptoms. Hydrodistention was performed, and crack and petechial hemorrhage were found, and she was treated with tricyclic antidepressants and antihistamine. However, these treatments were ineffective. An allergy or autoimmune reaction was suspected as the pathogenesis due to eosinophilia and elevation of serum IgE levels. The patient was then treated with immunosuppressive agents. Although her symptoms were not sufficiently improved by single-agent therapy with prednisolone or tacrolimus, they were completely improved by their combined administration. This is the first case to report the effectiveness of combination therapy consisting of prednisolone and tacrolimus to treat PBS/IC.

Introduction

Painful bladder syndrome/interstitial cystitis (PBS/IC) is a severely debilitating disease of the urinary bladder. Symptoms include excessive urgency and frequency of urination, suprapubic pain, dyspareunia and chronic pelvic pain. The pathogenesis is unclear, although autoimmunity may play a role. There have been reports on the efficacy of steroid and immunosuppressive agents We report a case of severe PBS/IC that was not sufficiently improved by singleagent therapy, but was completely cured by combination therapy of prednisolone and tacrolimus.

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Case report

A 47-year-old woman became aware of frequent urination and intensive pelvic pain in February 2008. She had been medicated with tranilast and tranquilizers for depression and asthma, respectively. She was urinating at least 60 times per day when she visited our urology department. Urine analysis showed red blood cells (RBC) >100/high power field (HPF) and white blood cells (WBC) >100/HPF. A urine culture for bacteria was negative. Her bladder capacity was 50 mL or less, according to her voiding diary. Polymerase chain reaction targeting tuberculosis and urine cytology were both negative. A withdrawal of her regular medications did not improve the symptoms.

Hydrodistention and transurethral biopsy of bladder mucosa were carried out under spinal anesthesia. The bladder was distended up to only 120 mL of saline, and crack and petechial hemorrhage were found. Simultaneous histopathological examination of bladder mucosa revealed infiltration of neutrophils, lymphocytes, plasma cells and a small number of eosinophils, but mast cells were not shown. The symptoms, however, were not improved by hydrodistention.

She consulted another urologist who treated her with an antihistaminergic agent (cetirizine hydrochloride), tricyclic antidepressants and an antihistamine, as recommended by the guidelines for PBS/IC,^{1,2} but they were ineffective. She refused intravesical therapy with heparin or lidocaine.

She complained of more intense pelvic pain in April 2008, and was admitted to our emergency department. The results of a physical examination were normal. Laboratory data showed eosinophilia (WBC 10,900/µl, eosinophil fraction, 26%), elevation of serum IgE (3900 IU/mL), and a slightly elevated level of serum creatinine (1.6 mg/dL). Rheumatoid factor and antinuclear antibody were both negative. Urine analysis showed microscopic hematuria (RBC >100/HPF) and pyuria (WBC >100/HPF). Parasite eggs were negative in both urine and stool samples. Abdominal computed tomography (CT) showed marked thickening of the bladder wall (Fig. 1) and right mild hydronephroureter. Histopathological diagnosis and other laboratory findings suggested an immunoreactive disorder of the urinary bladder. We therefore decided to undertake immunosuppressive treatment for this persistent PBS/IC with intervening eosinophilia. Oral pred-

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Fig. 1. A computed tomography revealed circumferential thickening of the bladder wall.

nisolone (30 mg/day) was started. The frequency of urination decreased gradually and the pelvic pain was reduced. When the dose of prednisolone was reduced to 10 mg per day, urination frequency increased and the pelvic pain worsened. We therefore started oral tacrolimus administration (2 mg/day). Voiding decreased to 15 times per day and the pelvic pain was relieved. The symptoms worsened again when cessation of prednisolone was attempted. Therefore, combined therapy consisting of 10 mg of prednisolone and 2 mg of tacrolimus per day was started. The pain gradually improved, as did the thickening bladder wall and the right hydronephroureter on CT scanning 8 days after initiation of the combination therapy (Fig. 2). The microscopic hematuria and pyuria were completely cured. She was discharged 2 weeks after starting the combination therapy. She continued to be treated as an outpatient, and the doses of both prednisolone and tacrolimus were reduced. Tacrolimus and prednisolone were stopped in October 2008 and January 2009, respectively. Both serum IgE and eosinophils decreased gradually and currently are within their normal ranges. As of one year after the cessation of immunosuppressive agent administration, there are no signs of recurrence and her voiding status is good (Fig. 3).

Discussion

The etiology of PBS/IC remains uncertain, but various factors or mechanisms are involved, including reduced bladder surface mucin, occult infection, neurogenic alteration, mast cell



Fig. 2. Thickening of the bladder wall disappeared.

activation, toxic substances in the urine and autoimmunity.³

We encountered this disorder, with an underlying of allergy or autoimmune reaction, because of eosinophilia and elevation of serum IgE level. The patient's symptoms and medical history were atypical for PBS/IS. Symptoms of most PBS/IC cases are gradually exacerbated at the onsets, however, markedly frequent urination and intolerable intensive pelvic pain suddenly developed in this case. Additionally, drug-induced IC was initially suspected since she had been taking various medications (antidepressants, minor tranquilizer, antiepilepsy agents and sleep agents). Although her symptoms and medical history were atypical for PBS/IC, similar diseases (i.e., cancer, infection, urethral diverticulum, urogenital prolapsed, endometriosis) for PBS/ IC were excluded, so the diagnosis of PBS/IC was made. Neither the symptoms nor objective findings were resolved after discontinuing these medications, so the patient was further treated with immunosuppressive agents, which finally brought her symptoms under control. Our experience indicates that some PBS/IC patients can be well-managed with immunosuppressive treatment.

Recent reports have indicated that multimodal oral therapy, intravesical therapy and surgical intervention are treatment options for PBS/IC. The target of oral therapy is glycosaminoglycan (GAG) layer dysfunction, mast cell abnormalities and neurogenic inflammation.⁴ Pentosan polysulfate (PPS) remains the cornerstone of drug therapy for most patients. Although the exact nature of PPS on the bladder is not completely clear, it is believed to function by coating the bladder lining, re-establishing normal GAG layer function and decreasing potassium leak into the interstitial



Fig. 3. Clinical course of the patient, showing the number of urinations and voiding volume.

space.⁵ We have no experience with this treatment, since it is not yet approved for use in Japan. Antihistamines potentially inhibit mast cell degranulation,³ but were ineffective in our case. Tricyclic antidepressants are also effective for pain modulation due to their ability to decrease serotonin and norepinephrine reuptake in the central nervous system and to stabilize mast cells; they also have a moderate anticholinergic effect.⁶ However, neither treatment was effective in our case.

Several intravesical agents, such as dimethyl sulfoxide, heparin and anesthetic agents, are indicated for patients who do not respond to oral therapy.³ Additionally, the effectiveness of hydrodistention when conservative approaches have failed has been reported.¹ But in our case, the bladder was distended only to 120 mL under lumber anesthesia, and the symptoms did not improve after hydrodistention.

In 1953, Dees reported that steroids were effective for interstitial cystitis.⁷ In 2005, Soucy and Gregoire reported that a trial of prednisolone should be considered in patients with severe ulcerative interstitial cystitis unresponsive to conventional treatment.⁸ In our case, prednisolone was transiently, but incompletely, effective so an immunosuppressive agent was also administered. The effectiveness of immuno-suppressive agents has been reported. In 1976, Oravisto

and Alfthan described their experience with azathioprine in 38 patients, and reported the pain disappeared completely in 22 and the pollakiuria was alleviated in 20.9 In 1996, Forsell and colleagues reported that cyclosporine (CyA) in 11 patients resulted in a decrease or total disappearance of pain in 10 patients, allowing for a larger volume of urine storage.¹⁰ In 2004, Sairanen and colleagues reported that CyA treatment was safe and effective, and its therapeutic effect was maintained in the long term.¹¹ CyA inhibits T cell activation by blocking the transcription of cytokine genes¹² and stabilizing mast cells.¹³ The biological activity of tacrolimus, another calcineurin inhibitor, is 10 to 100 times stronger than that of CyA.14 We attempted tacrolimus in combination with prednisolone, and found it to be highly effective. Although the exact mechanism is still unknown, our experience indicates the treatment may be successful for a certain population of PBS/IC patients.

Conclusion

We experienced a case of severe PBS/IC that was completely cured by combination therapy of prednisolone and tacrolimus. This is the first case to report the effectiveness of their combination therapy for PBS/IC. Competing interests: None declared.

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