

Case Report

Is interstitial cystitis an allergic disorder?: A case of interstitial cystitis treated successfully with anti-IgE

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Abstract Interstitial cystitis (IC) is a chronic disorder diagnosed by symptomatology of pelvic pain and urinary frequency, which are extremely variable and unpredictable fluctuating among patients. IC has recently been found combined with some allergic disorders and histopathologic abnormalities resembling that of allergic disorders, including mast cell activation, histamine release and eosinophil infiltration. Therefore, it could be cautiously postulated that IC is one of the allergic disorders of the urogenital system. A 28-year-old Caucasian female patient, who was diagnosed with asthma and allergic rhinitis, suffered from bladder symptoms of frequency, urgency and pelvic pain for the past 3 years. The symptoms disturbed her every day and were intractable for treatment. Urologists concluded that she had interstitial cystitis. Specific immunotherapy (SIT) was recommended for her allergic symptoms. While taking specific immunotherapy, she had anaphylaxis. She still had the reaction even with the 1000-fold diluted shot of SIT. Omalizumab was used for her allergic symptoms and possible prevention of anaphylactic reaction to SIT. Interestingly, she reported that her urogenital symptoms had subsided since omalizumab had been started. According to the published literature, we postulate that interstitial cystitis might be one of the IgE mediated, mast cell driven allergic disorders of the urogenital system. Therefore, in this case, the patient's bladder symptoms are successfully controlled primarily by anti-IgE therapy and the improvement could be maintained by SIT. We report, for the first time, a case of interstitial cystitis with allergic rhinitis and asthma, successfully treated by anti-IgE therapy and specific immunotherapy.

Key words interstitial cystitis, anti-IgE, immunotherapy, hypersensitivity, asthma.

Introduction

Interstitial cystitis (IC) is a chronic debilitating bladder disorder characterized by suprapubic and urethral pain and urinary frequency, which can be extremely variable and fluctuate unpredictably between patients. Most symptoms cannot be explained by any known urologic or other systemic pathology.¹ The consensus criteria are frequently used to diagnose IC,² although interstitial cystitis is diagnosed most frequently by exclusion of other disease.

Interstitial cystitis has been found in combination with some allergic or autoimmune disorders and histopathological abnormalities resembling allergic disorders, including mast cell activation, histamine release and eosinophil infiltration. According to the findings in the present study, IC might be cautiously suggested as an allergic disorder of the urogenital system in some cases.

Omalizumab, a chimeric monoclonal anti-immunoglobulin E antibody (anti-IgE), has recently become available and is indicated for the treatment of intractable allergic asthma. It might act by eliminating serum IgE, preventing attachment onto mast cells, and decreasing histamine release from mast cells. Anti-IgE in combination with

specific immunotherapy is reported to reduce the symptom load of seasonal allergic rhinitis.³

Immunotherapy with specific allergens has been used as a curative modality for some allergic disorders. Norman provides a better understanding of its mechanisms of action, reducing serum concentration of specific IgE, increasing IgG4 concentration, and changing the cytokine profile to allergenic exposure.⁴ Some modifications have been attempted to overcome the inconvenient injection schedule and the risk of adverse reaction, most of which are mediated by IgE. The anti-IgE is effective in preventing or minimizing the IgE-mediated severe reaction during immunotherapy.

We report on a patient affected by IC, allergic rhinitis and bronchial asthma, whom we treated with omalizumab (Xolair, Novartis). The rhinitis and bronchial asthma improved, the symptoms of IC decreased, and the patient was able to return to study and a normal life.

Case report

A 28-year-old Caucasian female patient was referred for evaluation of recently aggravated chest discomfort and wheezing. She was a married law student, but she stopped studying because of her bladder symptoms. For the past 3 years, she had been suffering intermittently from nausea and vomiting combined with lower abdominal and pelvic pain, which occasionally would awaken her from sleep.

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She had bladder symptoms of frequency, urgency and dysuria every day, which caused her to stop studying and to avoid coitus. Prior investigations including colon fiberoscopy and pelvic examination revealed no abnormality. She had been referred to a urologist for further evaluation of her bladder symptoms. She had sterile urine in several culture trials and urinalysis was within normal ranges. Her symptoms did not respond to non-steroidal anti-inflammatory drugs or to medications for motility control of the gastrointestinal and urogenital systems. She had undertaken hydrodistention as a therapeutic trial from another urology specialist, with no improvement. She had normal complete blood cell count and serum chemistry. Her urologist concluded that she had interstitial cystitis after intravenous pyelogram and cystoscopic examination, the latter of which showed glomerulations and some discrete bleeding ulcers (Hunner's ulcer) on the bladder wall (Fig. 1).

In the allergy clinic, she complained of a perennial stuffy and runny nose, and intermittent shortness of breath that had started several years before but had become exacerbated recently. Physical examination revealed that she breathed shallowly to avoid dry cough. Her oropharynx was clear and nasal mucosa looked erythematous and edematous with some clear discharge. Chest auscultation revealed wheezing during expiration. Routine laboratory tests including blood cell counts and chemistries were within normal limits. In spirometry, her FEV1 was 2.43 L (75% of predicted value), which increased to 3.07 L in the bronchodilator trial. Skin prick tests with 60 common environmental allergens showed that she was sensitized to: timothy (3+), bahia (3+) and perennial rye grass (3+); penicillium (3+); house dust mite (2+); cat dander (2+); cockroach (3+); and homodendrum (2+). The control (histamine, 1 mg/mL) gave a reading of 2+ and the diluent was

negative. The total IgE concentration in serum was 653 IU/mL (normal range, 0–158 IU/mL).

Specific immunotherapy with allergen extracts mixed according to her skin prick test results was recommended along with symptomatic treatment of her allergic rhinitis and asthma. She had an anaphylactic reaction to the first immunotherapy injection, which was a 1000-fold diluted dose compared with the maintenance dose. Approximately 10 min after the injection, her blood pressure dropped and she felt lightheaded with shortness of breath and wheezing. She had the same reaction to the immunotherapy diluted up to 100 000-fold. Omalizumab was given to control her asthma symptoms and to prevent adverse reaction to the immunotherapy. Three hundred milligrams of omalizumab was injected subcutaneously (150 mg in each arm) every 4 weeks. Specific immunotherapy was started successfully after the fourth week of omalizumab injection, with no adverse reaction. Against medical advice, she missed an omalizumab injection after 7 months of injections, without any adverse reaction during immunotherapy. Interestingly, she reported that most of her urogenital symptoms had stopped after the onset of omalizumab, even after she skipped one dose. She was delighted to sleep all through the night without urgency and frequency, which let her go back to school and continue studying. She was referred to a urologist for follow-up cystoscopic examination, which showed decreased glomerulation and no ulcer (Fig. 2). She is now on maintenance immunotherapy and most of the symptoms of allergic rhinitis and bronchial asthma are

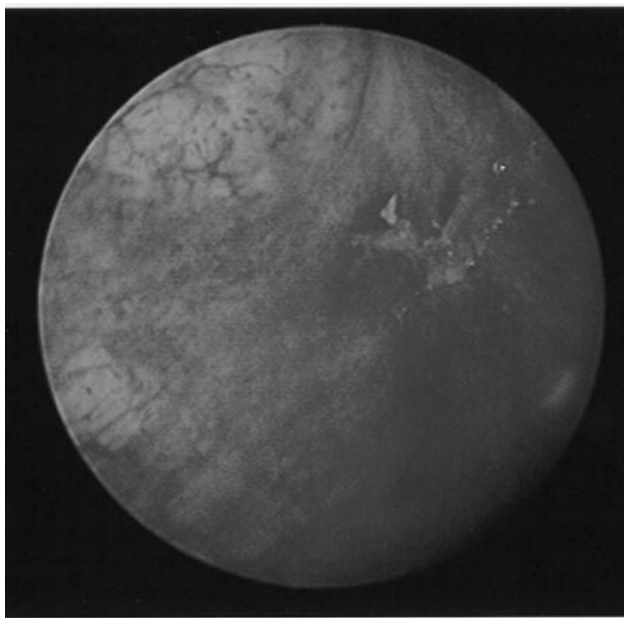


Fig. 1 Glomerulations and a discrete, bleeding area (Hunner's ulcer) were seen on patient's bladder wall in cystoscopic examination before omalizumab treatment.



Fig. 2 Significantly less glomerulation and no ulcer were observed in cystoscopic examination, taken 7 months after omalizumab treatment.

under control with a short-acting bronchodilator and oral antihistamine on a p.r.n. basis. In a recent interview, she reported that she has experienced no urogenital symptoms, has returned to law school, and plans to have a baby. The total IgE concentration at this visit had declined to 168 IU/mL.

Discussion

In allergic inflammation, allergen binding to allergen-specific IgE attached on the FcεRI of mast cells and basophils causes release of various inflammatory mediators from mast cells and basophils. Designed to bind free IgE, omalizumab rapidly reduces free IgE concentration in the circulation, which significantly reduces the number of high-affinity IgE receptors on mast cells and basophils and prevents allergen-induced activation of mast cells and basophils.^{5,6}

The diagnosis of interstitial cystitis depends mainly on the patient's subjective symptoms. Interstitial cystitis is also known as painful bladder syndrome. The widely accepted criteria from the National Institute of Diabetes and Digestive and Kidney Disease list only the exclusion criteria and cystoscopic findings, which are typical glomerulations. Hunner's ulcer is referred to the only pathognomonic finding, and no characteristic histopathological finding is helpful for diagnosis.⁷ In our experience, most of the bladder epithelial lining looks normal, although cystoscopy can show some shallow ulceration. Except for an increased number of mast cells infrequently reported in biopsy samples, non-specific findings are common. Because of slow wound healing and aggravated symptoms after biopsy, the results are usually disappointing. In the evaluation on interstitial cystitis, the objective data on the extent of the patient's improved symptoms are hardly shown, but depend only on the patient's expression.

No treatment of choice has been proven through large-scale, double-blind, placebo-controlled trials. Oral⁸ and intravesical⁹ pentosan polysulfate therapy and intravesical Bacillus Calmette Guérin therapy¹⁰ have been effective in small-scale studies, although this issue is still debated.^{11,12}

Recently, interstitial cystitis has been suggested to be an allergic disorder of the urogenital system, although there have been no large studies to support this suggestion. Yamada report that as many as 80% of 36 patients who had met the diagnostic criteria for IC had allergic disorders.¹³ Mast cells and eosinophils were increased in vesical biopsy specimens from 6 patients who had concomitant bronchial asthma and IC. In an intravesical provocation trial with IgE RAST-positive antigens, 4 of 16 patients were positive for histamine release.¹⁴ Degranulated mastocytosis is reported in a bladder biopsy of a patient with IC and chronic urticaria-angioedema.¹⁵ Although there are few double-blind placebo-controlled studies, as many as 50% of IC patients might have temporary remission unrelated to therapy. IC is now treated with antagonists of mast cell-driven vasoactive and proinflammatory molecules, such as amitriptyline, hydroxyzine, cimetidine and montelukast.^{16,17}

Based on the published literature, we postulate that, in select cases, IC might be an IgE-mediated, mast cell-driven

allergic disorder of the urogenital system. In the case reported here, the symptoms of asthma and rhinitis and bladder symptoms were successfully controlled by anti-IgE therapy. This improvement appears to have been maintained by specific immunotherapy.

We report a case of interstitial cystitis with allergic rhinitis and bronchial asthma, which was treated successfully with anti-IgE therapy and specific immunotherapy. We suggest that, in IC patients, allergic disorders should be investigated and anti-IgE therapy and specific immunotherapy might be considered as a second-line treatment. Investigations should be performed on the pathophysiology of IC and the effects of anti-IgE therapy and specific immunotherapy.

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