

Review

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Eosinophilic Cystitis and Interstitial Cystitis: may allergy be the reason?

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Allergic diseases have increased in prevalence during recent years. Although they impose numerous health and financial burden on patients and their family and also the society, they are to some extent preventable and manageable. While reviewing the literature to find any relationship between allergic disease as the familiar and preventable conditions and the two unfamiliar entities, named Eosinophilic Cystitis (EC) and Interstitial cystitis(IC); a significant number of reports were found about the etiological roll of atopy and allergy in the development of these conditions. Nevertheless this relationship is stronger concerning IC than EC. Referring to allergy as a contributing factor makes it more understandable and controllable. Although in order to reach a proper conclusion more thorough studies are required.

Keywords: Interstitial Cystitis; Hypersensitivity; Atopic Hypersensitivity; Eosinophilia; Humans; Urinalysis.

Running Title: Eosinophilic Cystitis and Interstitial Cystitis

Introduction

The role of immune system in development of many of the inflammatory urinary tract diseases is accepted. Allergic diseases causing inflammatory disorders are increasing in prevalence since the last 3 decades. Allergic diseases result from complex interactions between genetic predisposition and environmental factors. Seeking any relation between urinary tract disorders and allergic diseases as the etiological factors; the literature was reviewed and two main topics were selected to be discussed.

I- interstitial cystitis

Interstitial cystitis (IC) is a chronic disabling inflammation of the bladder characterized by suprapubic and urethral pain, urinary frequency and urgency, nocturia, with or without hematuria. It is a common disease mainly in women urinalysis shows white blood cells (WBC) and red blood cells (RBC), while the culture remains negative.

Lack of familiarity of IC by physicians and the use of inappropriate diagnostic approaches may result in a prolonged period between the onset of symptoms of patients and the accurate diagnosis of IC; and may cause inappropriate use of antibiotic in that period. 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 [1].

The diagnosis is based on a combination of chronic irritating voiding symptoms, sterile urine, characteristic cystoscopic findings and the exclusion of other diseases. Many patients have periods of remission and exacerbation. Symptoms may worsen in the perimenstrual period in about half of the affected women. Cystoscopically, IC is characterized by petechial bladder mucosal hemorrhages (glomerulations). Severe IC is

associated with reduced bladder capacity and in rare cases with the classic Hunner's ulcer [2]. There are many case reports describing IC in the literature:

- Yamada et al. presented a case series of 6 patients who had irritation during voiding and simultaneously asthma, allergic rhinitis or atopic dermatitis and one of them had ulcerative colitis. The total serum IgE concentration was elevated (250 IU/mL) in 3 patients. Specific IgE for common environmental allergens was positive in the skin prick test (5 of six patient had immediate positive skin test and 4 of six had in vitro positive IgE test [radio allergosorbent test = RAST]). The intravesical provocation test with the same allergens that the patients had tested positive in the RAST (RAST score > 2) was performed. All 4 patients developed bladder irritation within 30 minutes following infusion of the antigen into the bladder followed by the measurement of the urinary histamine concentration which showed elevation in each patient during the immediate 3-hour period after allergen provocation test [3].
- Again in another study done by Yamada et al, a 28-year-old woman presented with bronchial asthma concomitant bladder symptoms which made her avoid coitus along with intermittent nausea and vomiting and lower abdominal and pelvic pain for a duration of 3 years. She also had complaints of an allergic rhinitis several years before. Spirometric findings were in favor of asthma. Looking for an allergic diathesis, the skin prick test and serum specific IgE with common environmental allergens was performed and showed sensitivity to numerous grass pollens and a lot of the indoor allergens (penicillium, house dust mite, cat dander and cockroach)[4].
- Likewise Lee et al. reported a 28 year old female who presented with asthma and bladder symptoms including: urgency and dysuria which started 3 years ago. She also had complaints of a stuffy and runny nose and intermittent shortness of breath that started several years ago. The result of skin prick test demonstrated sensitivity to multiple environmental allergens. Immunotherapy with specific allergens as well as the symptomatic treatment for

allergic rhinitis and asthma was scheduled. She developed anaphylactic reaction during the multiple course of immunotherapy in spite of allergen dose reduction. In order to control the anaphylactic reaction; along with specific allergen immunotherapy she received Omalizumab (an anti IgE antibody) that resulted in no repeat of anaphylaxis and resolution of most of the urogenital symptoms. Omalizumab was continued for 7 months. On cystoscopic re-examination, glomerulation was decreased and no more ulcers were seen. According to the findings in the present study, IC might be cautiously suggested as an allergic disorder of the urogenital system in some cases [5].

- In a case control study performed by Bouchelouche et al. on a series of 9 patient with IC, he demonstrated that urine level of leukotriene E4 and eosinophil protein X in patients with IC are significantly higher than control group. It was previously proposed by the same author that Montelukast, as a specific inhibitor of cysteinyl containing leukotriene receptor I, which was usually used to treat allergic disease in the lung, can be effective for voiding symptoms and bladder pain in patients [6].

It was revealed by Bouchelouche et al. that leukotriene D4 can cause increased influx of intracellular free calcium in isolated human detrusor smooth muscle. Cysteinyl leukotrienes provoke histamine responses by engaging additional histamine receptors in immunologically relevant cells [7]. Interstitial cystitis has been found in combination with some allergic or autoimmune disorders and histopathological abnormalities resembling allergic diseases. According to the findings, it has been proposed that IC might be cautiously suggested as an allergic disorder of the urogenital system in some cases [3]. It is commonly thought that IC is associated with allergy on the basis of findings of increased numbers of infiltrating mast cells and eosinophils in the bladder wall, effectiveness of antihistamine and anti allergic drugs. Moreover, it was found that about half of IC patients have complications of allergic illnesses [4,5].

Allergic responses

Allergic responses can be classified as either immediate or delayed. Coombs and Gells further

classified the immediate response as type I, and delayed response as II, III or IV.

In type I responses, the antigen-antibody reactions primarily involve IgE which binds to mast cells, causes the activation of mediators such as histamine, serotonin and leukotrienes, and infiltration of various inflammatory cells such as eosinophils, thus resulting in damage of the tissue. Type II works by using antibodies IgG or IgM. Type III works using a complex of antigen and antibody which deposits on the endothelial surface and activates the complement system and class IV of hypersensitivity reactions are settled by cell mediated immunity, thus the main moderator in these kind of reaction is T lymphocyte [3].

Bladder wall and specially submucosa is chronically embedded with a large amount of T lymphocytes, plasma cells, eosinophilic leukocytes and mast cells in interstitial cystitis. Mast cells and eosinophils as the puissant inflammatory cells are alleged to a variety of hypersensitivity disease in many organ systems including: skin, lung and gastrointestinal tract. Mast cell activation and degranulation by specific (IgE binding) or nonspecific stimulant, initiate the release of a series of pre-stored mediators like histamine, heparin, trypsin, protease, phospholipase, chemotactic substances, cytokine and also leukotriene C4 and B4, prostaglandinG2, platelet activating factor, thromboxane and nitric oxide [8].

Subsequently, leukotriene C4 is converted to leukotriene D4 (Leukotriene D4 has induced bronchoconstriction in human) and eventually leukotriene E4 which is the end product of the cysteinyl containing leukotrienes and can be detected in the urine and would predicate a chain of allergic events. Cysteinyl leukotrienes are potent spasmogens, 1,000-fold greater than histamine. However, mast cells and eosinophils are the major source of cysteinyl containing leukotrienes in the urine; Thus, in almost any disease associated with tissue destruction, heavy mast cells and eosinophil infiltration, and activation are observed [6].

The release of leukotrienes and eosinophil protein X from mast cells and eosinophils in the bladder wall may have a significant involvement in the pathogenesis, symptoms and tissue damage of the bladder in patients with interstitial cystitis [6].

The serum concentration of eosinophilic cationic proteins, which cause tissue damage, and the urinary methyl histamine concentration have been reported to be elevated in patients with

interstitial cystitis, in other words pointing to the role of allergic responses. The eosinophil is also a potent inflammatory cell actively involved in almost all types of inflammatory processes. They exert their effect by secretion of the 4 cytotoxic proteins including: eosinophil protein X, eosinophil cationic protein (ECP), eosinophil peroxidase and major basic protein. Also leukotriene C4 and platelet activating factor are lipid based secretions of eosinophils [9].

However in all the above studies the patients suffering from interstitial cystitis demonstrated concomitantly, characteristic allergic diseases such as: asthma, rhinitis and atopic dermatitis; also, elevated serum IgE occurred in a number of cases. In addition positive specific IgE elevation in response to environmental allergens in a majority of cases was reported and eventually a number of cases who showed positive result in intravesical provocation with the same allergen as their skin prick test; all demonstrate an etiologic roll for allergy in developing the disease. In recent years, the number of patients suffering from allergic diseases has become more frequent due to environmental deterioration and the number of IC patients exhibiting complications of allergic diseases has also increased [3].

II- Eosinophilic cystitis

Eosinophilic cystitis (EC) is a rare inflammatory disorder first reported by Brown in 1960 who described the condition as eosinophilic granuloma of the bladder [10]. In this disease the muscle of the bladder is infiltrated by eosinophils. The incidence of EC is the same in both sexes, although a slight male predominance was reported among children [11]. The pathogenesis is generally ascribed to a regulatory disorder of the immune system, parasitosis, food and drug allergies, intravesical instillation of chemotherapeutic agents (Mitomycin or Candthiotepa), tuberculosis, malignancies and urinary tract catheterization as well as chronic catgut sutures, although it is mainly not understood [12,13].

Patients with EC usually present with irritative voiding symptoms including dysuria, frequency, urgency, hematuria, and suprapubic tenderness or even systemic symptoms. Some combination of microhematuria and pyuria is invariably present but eosinophils are rarely identified in the urinary sediment because they are rapidly degraded or there is little mucosal shedding [14]. Microscopic hematuria and pyuria may be imitator of the urinary tract infection however urinary culture

remains sterile.

Physical examination is usually unremarkable. Radiological findings include a bladder occupying lesion that mimics invasive bladder carcinoma and dilation of the upper urinary tract. Symptoms of obstruction in the urine flow are usually found in cases with ureteral orifice involvement. Peripheral eosinophilia is found in nearly 40% of patients with EC. Cystoscopic biopsy which shows eosinophilic infiltration of the lamina propria and muscularis in the acute phases and variable degrees of fibrosis in a more long standing disease will confirm the diagnosis [11,12,15].

Importantly, children can present with a palpable suprapubic mass or a bladder lesion similar to malignancy, emphasizing the importance of biopsy before thinking of malignancy. Biopsy showing eosinophilic infiltration of the lamina propria and muscularis are diagnostic. However, pathological examination can be misleading because specimens commonly resemble nonspecific chronic inflammation [16].

Hence, in cases where a biopsied bladder mass is diagnosed as chronic inflammation it is advocated to alert the pathologist to the possibility of eosinophilic cystitis using Giemsa stain for determination of the presence of eosinophils and muscle necrosis. Diagnosis of eosinophilic cystitis commonly requires cystoscopy and biopsy; procedures generally limited in the pediatric population, thus it is highly probable that the true incidence of eosinophilic cystitis is underestimated [16]. The clinical and histopathologic presentation may vary from mild inflammation to chronic bladder fibrosis with resultant renal insufficiency [17]. A bimodal age of presentation with a primary peak between 3 and 4 years and a secondary peak at 11 years is suggested for pediatric EC [18]. EC has been described to a lesser degree in the pediatric population. Discrepancies of many facets of disease between adults and the pediatric population make the diagnosis a dilemma. As mentioned before this form of cystitis is also difficult to diagnose without cystoscopy and subsequent bladder biopsy. Nearly 58 pediatric patients have been reported in the literature, most as part of a small case series [18]. Urinalysis in EC commonly shows proteinuria and microscopic hematuria. Urine cultures are usually sterile. (19) Because of this variable presentation, EC is rarely encountered in children and often misdiagnosed, which results in time loss, hence, the practitioners caring for pediatric patients must be familiar with this diagnosis [13].

Eosinophilic cystitis, although rare and mysterious, should be considered in any child with irritative voiding symptoms and radiologic evidence of bladder wall thickening or a mass [17]. A series of case reports regarding this disease were published which are as follows:

- Yu et al. presented a 47-year-old woman with bladder symptoms, gross hematuria, suprapubic pain during urination and nocturia. She was suffering from a chronic asthma and presented with exacerbation of asthma simultaneously with bladder symptoms. RBC in urinalysis and eosinophilia were detected but urine culture was normal. A mass with irregular borders in the bladder wall with mild dilation of the right renal collecting system was disclosed on ultrasound. A polypoid lesion was found in cystoscopy at the right ureteral orifice and eventually tissue biopsy uncovered infiltration of eosinophils, along with focal muscle necrosis and fibrosis, compatible with the diagnosis of EC. Perceiving the association with asthma, she received fluticasone and Montelukast. After 4 weeks of treatment urinary and respiratory symptoms were alleviated and bladder symptoms had dissolved [12].
- In the pediatric population, Spark et al. also reported a series of 4 children including 3 females and 1 male aged 5 days to 18 years (5 days, 1 month, 7 years, 18 years) who demonstrated the special features of EC compared to adults. Bilateral hydronephrosis due to a suprapubic mass was the presenting sign in both of the infants and the two older patients both had dysuria while the 18 years old one also complained of fatigue, flank pain, and hematuria. Significant peripheral eosinophilia was noted in only 2 of the 4 patients and only one patient had eosinophiluria. Diagnosed in all patients was carried out using cystourethroscopy and biopsy. Similar to other pediatric patients in the literature, the common presentation in infancy appeared to be a palpable suprapubic mass and infectious process while the older children presented with irritative or constitutional symptoms. One of the cases presented as a pan urothelial involvement in a descending pattern, beginning with allergic interstitial nephritis and

hydronephrosis followed by the development of EC during a period of several months. Another case presented with urinary retention and went on to show refractory disease in spite of receiving appropriate treatment [18].

- An 8-year-old male presented by Taktak et al. who was admitted due to intermittent gross hematuria and dysuria of 1 month's duration. He had received several types of antibiotics despite negative urine cultures before admission. Laboratory data showed peripheral eosinophilia (10%) and markedly elevated serum IgE (1,050 IU/ml). Cystoscopy findings were in favor of EC [19].
- In another study by Thompson et al. a series of 4 patients with a mean age at presentation of 10.8 years and a male-to-female ratio of 3:1 were presented. All 4 patients presented with irritative urinary symptoms, 3 had dysuria and/or gross hematuria and 2 had urinary frequency, lower abdominal pain and/or urinary tract infection. Three patients had allergic diseases (asthma, allergic rhinitis, etc), and allergen skin testing was positive in 2 patients. A bladder mass mimicking malignancy was documented in 2 patients on pelvic ultrasound. Three cases demonstrated symptom resolution with conservative management, while case 4 represented an unremitting process that progressed to bladder augmentation [16].
- Mallat et al. reported a 30-year-old patient presenting with difficulty voiding, slow stream of urine, bladder symptoms and enuresis for 2 years with gross hematuria in the last 2 months. The patient also complained of intermittent abdominal pain and tenderness in the right upper quadrant for the last few months. An abdominopelvic ultrasound revealed an echogenic and diffuse wall thickening of the left side of the urinary bladder with moderate dilatation of the upper urinary tract. CT scan showed a tumor in the bladder. Moderate dilatation of the left upper urinary tract, lymphadenopathy and microlithiasis with thickening of the gallbladder wall was noted. A diagnosis of tumor of bladder and chronic cholecystitis with cholelithiasis was made. Laboratory tests on admission revealed a WBC count of

8600/mm³ with an eosinophil count of 33% (normal 0%–4%). Serum IgE level was 550 U/L. The serum amylase level was 94U/L (normal 25–115U/L). Urine cytology showed no malignant cells. Urine cultures were negative. Cystoscopic findings showed, a large papillary and solid lesion on the left side and biopsy revealed focal erosion. Diagnosis of eosinophilic cystitis was made [20].

- Sterret et al. reported a six-year-old boy who presented with a 4 day history of incontinence and dysuria. A computed tomography scan showed a polypoid mass arising from the posterior wall of bladder. Transurethral bladder biopsies revealed infiltrating eosinophils. He continued taking corticosteroids and antibiotics for 5 weeks and also montelukast sodium after 4 weeks of the initiation of the disease up to 6 months. During this period several attempts to discontinue the montelukast sodium resulted in recurrence of his dysuria. Skin test showed reaction to trees and weeds suggesting an environmental allergy as a contributing factor. Eosinophilic cystitis has been shown to relapse and progress more often in adults, suggesting that observation may be a suitable treatment option in children. Peripheral eosinophilia may be an ominous sign, however, suggesting that the disease may require additional treatment in these patients [17].
- Van den Ouden described a recurrence rate of 28% in a review of 135 patients diagnosed with eosinophilic cystitis [11].
- A case report by Kim et al. 3 patients had also suffered from eosinophilic gastrointestinal disorders. One of them who was an 81 year old man; suffered from ascites along with a three-week history of dysuria, abdominal pain with suprapubic tenderness, and distension. Contrast-enhanced computed tomography (CT) showed marked and diffuse bladder wall thickening and generalized edema in the jejunum and ileum. The second case was a 40 year-old man with intermittent diffuse abdominal pain for 7 days and no bladder symptoms in whom ultrasonography showed the multiple ill-defined echogenic nodules of liver and diffuse wall thickening of the

distal ileum and urinary bladder. Large bowel and bladder biopsy found numerous infiltrating eosinophils in the mucosa and submucosa. The third one was a 38-year-old man with diffuse abdominal pain with distension and urinary frequency for 10 days. Contrast-enhanced CT scan showed diffuse, marked bladder wall thickening of and multifocal segmental thickening of the small intestine. Eosinophilic cystitis and eosinophilic colitis were confirmed by cystoscopic and colonoscopic biopsies [21]. In a previous report the association of EC with Eosinophilic gastrointestinal disorders was expressed in 4.5% of cases of EC [11].

- There is also a recent report of a female case with eosinophilic gastroenteritis who presented with acute pancreatitis due to an egg allergy in whom all symptoms improved after cessation of egg products [22].
- Another case reported by Sano et al. was a 5-year-old boy who was referred with a complaint of micturition pain and frequency for 10 days. Urinalysis was unremarkable. The plain CT showed an irregularly thickened bladder wall and ascites. Biopsy of the bladder showed many eosinophils and no evidence of malignancy.

The number of eosinophils in the blood was 6700/mm³ and it was 56% of the white blood cells. Eosinophilia was also seen in his nasal discharge (12% of the cells were eosinophils) and bone marrow analysis showed a copious number of mature eosinophils [23].

The presentation of EC is varied and diagnosis requires high suspicion. Cystoscopy and biopsy is needed to establish the diagnosis as there is no typical appearance of the lesions or presenting signs/symptoms. Any patient presenting with unusual or recurrent episodes characterized by lower urinary tract symptoms should be evaluated. Any findings of a bladder mass in these patients should particularly rise the suspicion for EC and should be evaluated [18]. Eosinophilic gastroenteritis, reflux in the urinary tract system, severe hematuria which requires blood transfusion or salvage cystectomy, eosinophilic ureteritis, renal insufficiency and rupture of the urinary bladder are rare complications associated with eosinophilic cystitis. The few patients with progressive EC who do not respond to medical

therapy or transurethral resection may be considered for more radical procedures, such as partial/total cystectomy or augmentation [19].

There has been no consensus on diagnosis and treatment of the disease, however, Yamada *et al.* proposed a definition of EC as: (i) there are more than 20 eosinophils in each of five high power field in the tissue specimen; and (ii) more than 30% of round cells in the field are eosinophils [23]. Eosinophilic cystitis is a poorly understood inflammatory condition of the bladder. The cause of eosinophilic cystitis is still unclear [20]. However, many etiologies have been proposed, such as allergy, trauma to the bladder, atopy, surgery, intravesical mitomycin, drugs, recurrent urinary tract infection, vesicoureteric reflux, and food, such as tomatoes, coffee, and carrots [19].

Among all the etiologic factors an allergic response is the most probable. Asthma and celiac disease are also known to be associated with EC [24]. An association between EC and allergy has been previously reported in the literature; since five of the 24 reported patients had allergies [25].

In other cases reported in the pediatric population, 18 (33.3%) gave a history of other allergic conditions including seasonal or environmental allergies, medication allergies, and celiac disease. While in a recent study, a total of 4 (7.4%) patients had a diagnosis of chronic granulomatous disease. Twenty seven of the 54 patients (50%) demonstrated either a significant eosinophilia or eosinophiluria. Thirty five patients (64.8%) presented with irritative urinary symptoms while 15 (27.7%) had obstructive symptoms. The remaining patients had variable presentations and incidental findings leading to an eventual EC diagnosis. Interestingly recent case series have shown a coalition near 50% between EC and allergy [13].

Any patient presenting with unusual or recurrent episodes characterized by lower urinary tract symptoms especially those with a prior history of allergic conditions of any sort; should trigger the diagnosis of EC. Looking for a history of allergic conditions should be a standard part of the work up in all patients, but it seems particularly important in this group of children [18].

Pathogenesis of EC

It is believed that allergy is the main originator in EC. When the antigen enters the bladder it will cause B lymphocytes to produce IgE which will in turn bind to mast cells. Mast cells coated by IgE are sensitized and later if exposed to the same antigen will result in release of leukotriene (LTC₄)

and LTD4) and histamine, which will affect the bladder tissue. The antigen-antibody complex causes secretion of interleukin 5 (IL-5) and eotaxin by Th2 lymphocytes to release, which cause eosinophil aggregation.

Activation of mast cells will lead to the release of histamine and other mediators which can cause acute allergic reaction. Activated eosinophils will cause the extracellular release of a number of potent cytotoxic proteins such as eosinophil cationic protein (ECP), which are believed to play a role in the development of subacute and chronic symptoms of allergy [26]. Eosinophiles are the source of 4 cytotoxic proteins [9] among them the most important is ECP. The most conspicuous function is cytotoxic activity, which most likely is due to the capacity of ECP to make pores in cell membranes. Another one is the interaction with components of the coagulation cascade leading to acceleration of the coagulation cascade and thrombo-embolic phenomena. It is quite apparent from the above that ECP has a multitude of potent biological activities, some of which may be quite detrimental to the organism [27]. In one study the urinary level of ECP was used as a marker for disease depistage [23]. It has been appreciated for a while that tissue eosinophilia and eosinophil degranulation is commonly associated with fibrotic disease.

Eosinophils are implicated as a source of several other fibrogenic cytokines and modulators of remodelling such as fibroblast and smooth muscle cell mitogen, heparin binding epidermal growth factor-like growth factor (HBEGF), nerve growth factor (NGF) and TGF- α . IL-4 and IL-13, both predominantly Th2 cytokines, are also produced by eosinophils. IL-13 can induce fibroblast differentiation into myofibroblasts with activation of collagen production. IL-13 leads to subepithelial fibrosis and goblet cell hyperplasia and secretion [28].

Chronic eosinophilic inflammation has been associated with tissue remodeling in a number of disease states including the hyper eosinophilic syndrome (HES), asthma, and, more recently, eosinophilic esophagitis (EoE) A number of pro-fibrotic and pro-angiogenic factors are elevated in EoE including TGF β 1, CCL-18, FGF-9. TGF β 1 appears to be a master regulator of end organ dysfunction in EoE and can cause esophageal fibrosis and smooth muscle contraction; thus disease duration, especially untreated disease duration, increases the rate of strictures [29].

The eosinophils will secrete cationic protein when activated by leukotriene and IL-5 which then leads

to an inflammatory reaction and will result in fibrosis of the detrusor muscle.

Asthma is the allergic airway inflammation which can also cause systemic eosinophilia. Since the body is filled with cytokines in asthma patients may stimulate the chemotaxis of eosinophils in the urinary tract. In a case reported by Yu et al. the patient was diagnosed with EC when she was experiencing an asthma exacerbation; which may support the above hypothesis.

Corticosteroids are shown to be effective in several EC cases due to their strong anti-inflammatory effect by decreasing eosinophilic action and preventing phospholipid release.

Leukotrienes formed by inflammatory cells cause eosinophil recruitment and activation in EC. Montelukast is a leukotriene receptor antagonist and has been used for the treatment of asthma. It could also be used for treatment of EC due to its selective inhibition on leukotriene receptor mediated response [12]. Sterrett reported successful control of the disease by using montelukast in a pediatric patient with the diagnosis of EC [17].

Eosinophilic gastroenteritis (EG) is a chronic inflammatory disorder of the gastro intestinal tract with repeatedly reported varying degrees of eosinophilia in blood and several tissues in which there are increasing data in favor of food allergy as an etiological factor [30,31]. There is a recent report of in a female case with Eosinophilic gastroenteritis presented with acute pancreatitis due to an egg allergy in whom all symptoms improved after cessation of egg product [22]. Eosinophilic infiltrations maybe the final pathway by which endogenous and exogenous allergens cause IgE-mediated degranulation of mast cells and the release of eosinophilic chemotactic factors and cytotoxic cationic proteins that can induce tissue damage [16, 32].

Eosinophilic cystitis can be associated with eosinophilic infiltration of other parts of the body, including the liver and GI [21,33].

The first line of management usually comprises the removal of any suspected allergen, along with corticosteroids and antihistamines. One of theories is that corticosteroids, being an anti-inflammation drug, may speed up the resolution of symptoms by stabilizing lysosomal membranes [24].

In the treatment of adult eosinophilic cystitis cases, antihistamines, antibiotics, corticosteroids, non-steroidal anti-inflammatories, cyclophosphamide, doxorubicin, cyclosporine, mitomycin, radiotherapy along with

hydrodistension, Montelukast sodium and intravesical silver nitrate, could be used [13].

Due to the following reasons and having in mind all the above mentioned facts, IC and EC may be considered as a complication of allergy:

1- The strong association between symptoms of the bladder and of other organs displaying allergic reactions. This relation seems to be even more puissant in case of IC (in nearly 70% of patient with IC a history of a kind of allergic disease exist) compared to cases with EC (in about 50% of the cases a kind of allergic disease exist) [3,5,20,21].

2-Eosinophilic cystitis can be associated with eosinophilic infiltration of other organs, including the GI and liver. There are many reports about food allergens and even aeroallergens in the pathogenesis of the diseases [21,33].

3-The recurrence of the bladder symptoms after intravesical provocation with the same allergens to which, sensitivity had been previously shown by skin prick test or RAST [3].

4- Bladder symptoms improve following treatments including antihistamines and corticosteroids which implicate presence of the same pathogenesis as allergic diseases [13].

5- Regarding blood eosinophilia and eosinophilic infiltration in the tissue which occurs in many allergic diseases such as asthma, allergic rhinitis or atopic dermatitis as well as EC or even IC, a common pathogenic role can be assumed for all of these diseases [34]. It should be noted that the main effector cells that play a substantial pathogenic roll in developing Eosinophilic gastrointestinal disorder are eosinophils [29].

6-The elevated level of serum IgE (as a main humoral mediator of allergic reactions) mostly in IC and to a lesser extent in EC [19,20].

7- A Positive skin test against environmental allergens in most patients with IC and in a few cases of EC, which indicates sensitivity to common surrounding allergens (food and airborne materials) [3,5].

8-The resolution of bladder symptoms in one of the cases with IC, using Omalizumab (an anti IgE antibody) [5].

Thus, eosinophilic and interstitial cystitis may be considered the final common pathway for allergic cystitis. Involvement of different organs during allergy can be part of an allergic march and from a clinical aspect, bladder is also involved in the allergic march [4].

Conflict of Interest

None declared

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