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# Eosinophilic cystitis in males: A six year retrospective study

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**Abstract**
Eosinophilic cystitis (EC) is a non-neoplastic condition of the bladder associated with a strong female preponderance. Histologically, it is characterized by dense eosinophilic infiltrate in the mucosa and wall of the bladder. EC is associated with various benign and malignant genitourinary conditions. The present study was carried out to study the clinicopathologic features of EC in males.

**Materials and methods**
A retrospective study of all males patients diagnosed with eosinophilic cystitis between 2009 and 2015 was analysed. The histopathological features were correlated with clinical and cystoscopic findings.
Results: Twenty four males were diagnosed to have eosinophilic cystitis. Common presenting symptoms were haematuria and lower urinary tract symptoms. Associated genitourinary conditions included benign prostatic hyperplasia, renal cell carcinoma, prostatic adenocarcinoma, transitional cell carcinoma, urethral strictures, calculi and hydroureteronephrosis. The most common cystoscopy finding was erythematous mucosa. Biopsy findings revealed patients in acute and chronic phase along with few showing mixed features. These patients were managed with antibiotics, antihistaminics and steroids along with treatment of the associated condition.

**Keywords:** eosinophils, cystitis, cystoscopy

## Introduction

Eosinophilic cystitis (EC) is a relatively rare and poorly understood clinicopathological condition that has been reported in both adults & children; though fewer cases have been noted in the younger age group[1]. Similar to interstitial nephritis, EC has strong female preponderance[2]. This entity, first described in 1960[3, 4], presents with extensive eosinophilic infiltration in all the layers of bladder wall and may mimic a bladder tumor. The postulated hypothesis of the pathogenesis is disturbance in regulation of the immune system, but the exact cause remains obscure. EC can present with constellation of urological symptoms like increased frequency, dysuria, hematuria, suprapubic pain and urinary retention[5]. In the current study, we describe the spectrum of EC in males in the last six years in our department.

## Materials & Methods

This study was a 6 year retrospective study (2009-2015) retrieved from the departmental archives. The bladder biopsies of all male patients with EC were reviewed and categorized as morphologically consistent with EC if the infiltrate exceeded an average of 1 or more eosinophils per high power field (HPF). A minimum of 10 HPFs were counted to avoid potential spurious inclusion of inappropriate cases. Further, they were classified as EC in acute phase, chronic phase or mixed based on morphology. The medical records of all male patients were screened with special focus on patient age, clinical symptoms, cystoscopy findings, associated conditions and therapeutic approaches, wherever available.

## Results

Of the forty seven patients, 24 males and 23 females were diagnosed as eosinophilic cystitis on histopathology. The female patients were excluded from the study. The clinicopathological data of the 24 males diagnosed with EC on biopsy is tabulated in Table 1.The age ranged from 11 to 71 years with mean being 51.7 years. The most common presenting symptom was haematuria (14 cases) in isolation or with associated urinary symptoms. Lower urinary tract symptoms like dysuria, urge incontinence and urgency along

With obstructive symptoms including poor stream urine were also reported. Three patients presented with acute urinary retention. On cystoscopy, the most common feature observed was erythematous mucosa (8 cases) followed by polyp or nodules in 4 cases. Other nonspecific findings were trabeculation, ulcers, telengiectasia, diverticuli and thickened wall. Twelve of the 24 patients with EC had associated genitourinary conditions such as benign prostatic hyperplasia (4 cases; one of which also had renal cell carcinoma), prostatic adenocarcinoma (2 cases), transitional cell carcinoma (1 case), urethral strictures (1 case), calculi (2 cases) and hydroureteronephrosis (2 cases). Associated gastrointestinal tract diseases included one case each of tuberculosis and rectal adenocarcinoma.

**Table 1**: Clinicopathologic data of patients with eosinophilic cystitis

| Case number | Age | Presenting complains | Cystoscopy | Associated condition | Phase | Treatment |
|---|---|---|---|---|---|---|
| 1 | 44 | NA | NA | - | Acute | NA |
| 2 | 65 | Haematuria | NA | - | Chronic | Steroids |
| 3 | 58 | Haematuria | Erythematous areas | Stricture urethra | Chronic | Antihistaminics |
| 4 | 68 | Dysuria, Urgency | Erythematous areas | - | Mixed | NA |
| 5 | 71 | Haematuria | Erythematous areas in bladder | TCC bladder | Acute | Radical cystectomy |
| 6 | 11 | Dysuria, Haematuria | NA | - | Mixed | NSAIDS |
| 7 | 49 | NA | NA | - | Chronic | NSAIDS |
| 8 | 37 | Haematuria | NA | - | Chronic | Antihistaminics |
| 9 | 60 | LUTS | erythematous areas, trabeculations | BPH, RCC | Acute | NSAIDS |
| 10 | 71 | Haematuria, Acute retention | NA | BPH | Acute | Antibiotic. Anticholinergic and adrenergic receptor blocker |
| 11 | 70 | Haematuria, Acute retention | Erythematous nodules | - | Acute | Antibiotics |
| 12 | 50 | Haematuria, Acute retention | NA | - | Acute | NA |
| 13 | 56 | Haematuria, Urinary incontinence | Trabeculations, small polypoidal lesion in dome of bladder | Bladder stones | Chronic | Antihistaminics, Antibiotics |
| 14 | 52 | Abdominal pain, Acute retention | Small polypoidal lesions | left ureteric stone, HUN | Mixed | Stenting, Antibiotics |
| 15 | 72 | Urge incontinence, Urgency | Trabeculated mucosa | BPH | Mixed | Antibiotic. Anticholinergic and adrenergic receptor blocker |
| 16 | 29 | Haematuria, Dysuria | Erythematous mucosa | - | Chronic | Antibiotic |
| 17 | 65 | NA | NA | Prostate adenocarcinoma | Chronic | NA |
| 18 | 35 | Haematuria, LUTS | Erythematous mucosa | - | Mixed | NA |
| 19 | 54 | Hamaturia | Raised telengiectatic areas | Rectal adenocarcinoma, | Chronic | Antibiotic. Anticholinergic and adrenergic receptor blocker |
| 20 | 49 | LUTS, Retention | Trabeculation, erythematous mucosa | Neurogenic bladder with bilateral hydrouretronephrosis | Chronic | Antibiotic. Anticholinergic and adrenergic receptor blocker |
| 21 | 62 | Haematuria, Poor stream | Multiple diverticula | Prostatic adenocarcinoma | Chronic | Antibiotic |
| 22 | 8 | Haematuria, dysuria, urgency | Polypoidal lesion | - | Acute | Steroids |
| 23 | 48 | Suprapubic pain,Rretention | Erythematous mucosa | BPH | Acute | Antibiotic. Anticholinergic and adrenergic receptor blocker |
| 24 | 57 | LUTS, Lower abdominal pain | Thickened bladder wall | Intestinal tuberculosis | Mixed | Anticholinergic and adrenergic receptor blocker |

Abbreviations: NA - not available, LUTS - lower urinary tract symptoms, HUN - hydrourteronephrosis, BPH - Benign prostatic hyperplasia, RCC- Renal cell carcinoma, TCC- Transitional cell carcinoma.

Bladder biopsy of 8 patients showed eosinophilic cystitis in acute phase dense eosinophilic infiltrate, edema with or without ulceration and muscle necrosis. (Figure 1) Ten patients were in chronic phase with chronic inflammatory infiltrate, eosinophils with or without fibrosis. (Figure 2) Six patients showed mixed features of both acute and chronic phase. Superficial mucosa in 3 of the cases showed squamous metaplasia.

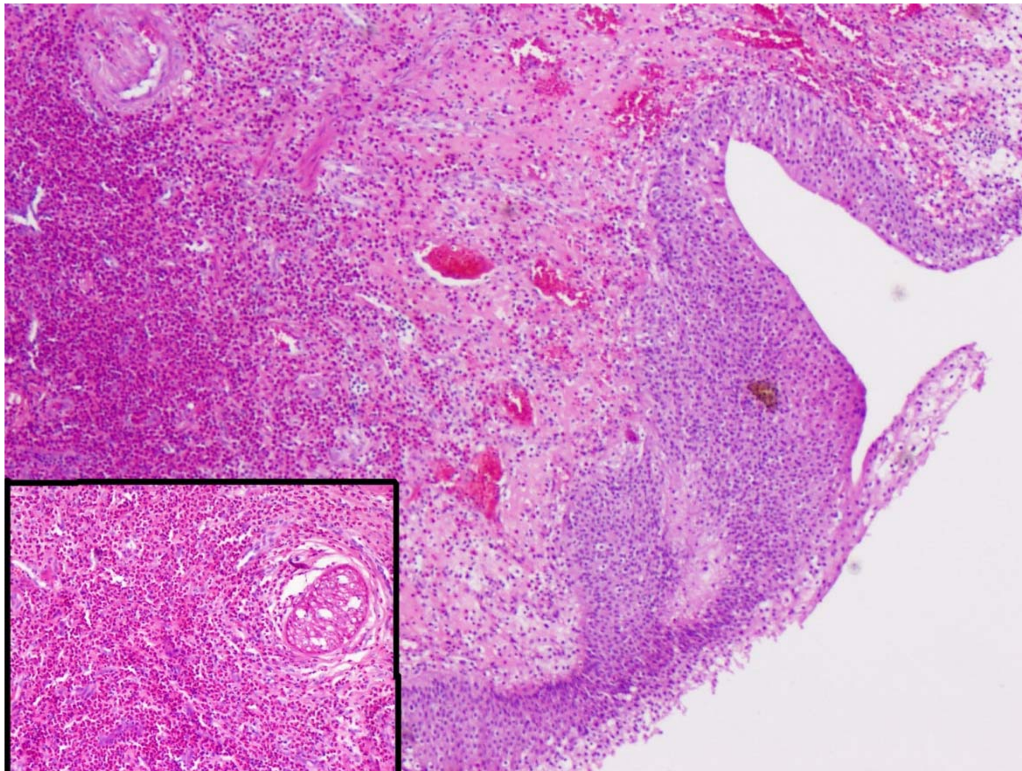

**Fig 1**: Acute phase of EC with squamous metaplasia of the urothelium along with edema, congestion and dense eosinophilic infiltration of the bladder wall (H&E, X2) Inset (H&E, X20)

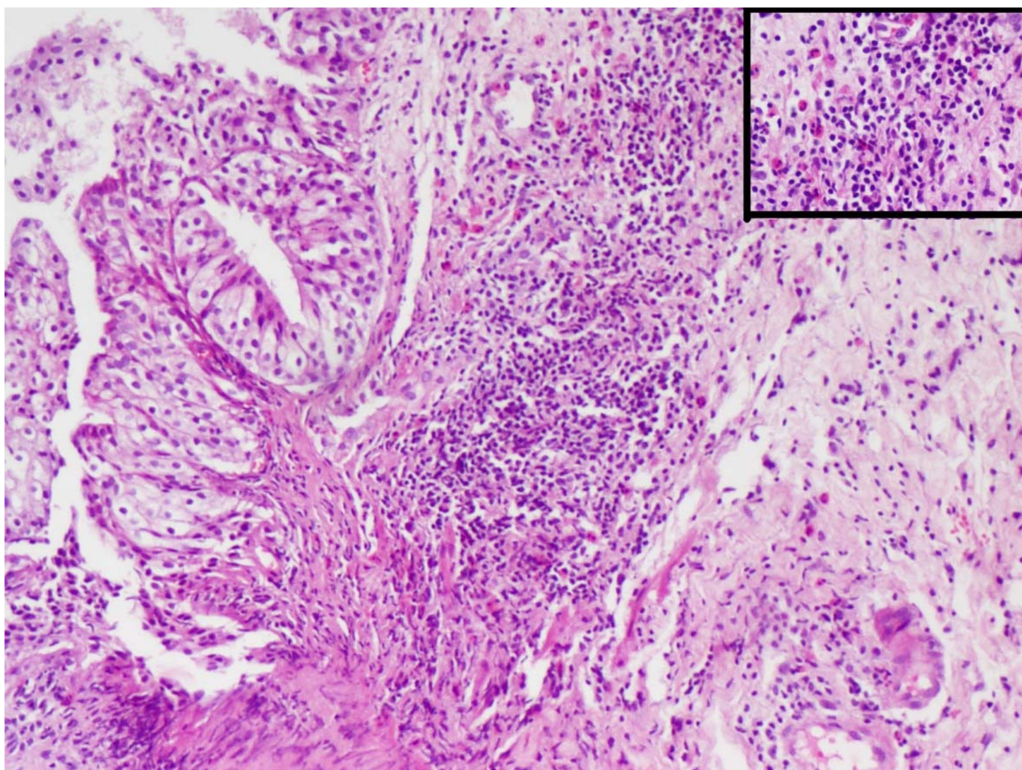

**Fig 2:** Chronic phase of EC with hyperplastic urothelium overlying bladder wall showing mononuclear inflammatory infiltrate and few eosinophils (H&E, X10) Inset (H&E, X40)

The treatment history for urinary symptoms was available for 19 patients. Twelve patients were treated with antibiotics, six of these also received a combination of antimuscarinic and adrenergic blocker to relieve urinary obstructive symptoms and one received antihistaminic. Two patients were treated with only antihistaminics, 3 received non steroidal antiinflammatory drugs (NSAIDS) and two steroids. Radical cystectomy was performed for the patient with TCC while stenting of the ureter was done for the patient with ureteric stones.

Follow up data was available for 8 patients receiving antibiotics, seven of which had no urinary complaints following treatment. One patient (case 14), developed pyelonephritis which later progressed to chronic kidney disease. Patients on antihistaminics, NSAIDS and steroids also were relieved of their symptoms following treatment.

**Discussion**

Eosinophilic cystitis is a rare condition, first described in 1960, independently by Palubinskas & Brown [3,4]. Many cases in adults and children have been identified till date, though frequency is much less in younger age group [6]. This condition may remain unrecognized especially in chronic phase and in males. The main pathological finding is dense and diffuse eosinophilic infiltration in all the layers of bladder wall. Though many aetiological factors have been proposed, the exact mechanism of this rare entity remains obscure, but certain immune dysregulation is thought to induce this process [7,8]. The pathogenesis suggest that there is binding of IgE to various antigens, thereby activating mast cell degranulation and eosinophils attraction and subsequently release of enzymes which cause damage to bladder wall.

Another hypothesis suggested is cytokine dysregulation[9], predominantly involving interleukin 4 and 5. These activate natural killer cells and T lymphocytes, favoring a transition from a $T_H2$ to a $T_H1$ response and beginning of chronic, smoldering phase of low grade inflammation and fibrosis. This condition is observed to be associated with injury, drugs (methicillin, warfarin, anthranilic acid, intravesical mitomycin, thiotepa, etc.), bacterial and viral infections and reaction to food/ vegetables and other allergens. As EC is associated with many factors, it is not a single distinct diagnostic entity, else it can be considered to be a response to various agents.

The patients with Eosinophilic Cystitis (EC) can present to outpatient department with variety of symptoms like increased urinary frequency, dysuria, gross/ microscopic hematuria, proteinuria, urinary retention and suprapubic pain [9]. A similar clinical presentation was seen in the present study. EC should be considered as a differential diagnosis in all the patients with frequent and unexplained bladder or other genitourinary complaints. In order to achieve at a correct diagnosis of EC and proper treatment strategy, all bladder biopsy material should be correlated with clinical history.

On cystoscopy, various findings can be observed like erythema, edema, ulceration to papillary lesions in bladder mucosa [10]. Sometimes, even an infiltrative mass-like lesion can be seen. The imaging studies in EC are non-specific. There can be thickening of the bladder wall, mimicking a tumor. Erythematous mucosa was the most common cystoscopic finding in our series.

Other laboratory parameters that can aid in the diagnosis of EC are proteinuria, microscopic hematuria, sometimes peripheral eosinophilia [11]. However, the gold standard for diagnosing EC is histopathological examination of bladder biopsy. But an important aspect to consider is the necessity of a deep biopsy to ensure correct diagnosis.

Eosinophilic Cystitis (EC) is described under two stages, i.e. acute and chronic phase. Biopsies may show mixed features of both acute and chronic phase [2,7,12,13]. Acute phase is characterized by a prominent eosinophilic infiltrate (1 eosinophil/ HPF in at least 10 HPF) associated with edema & sometimes muscle necrosis. Focal hemorrhagic areas can also be noted. However, in the chronic phase, which is often difficult to diagnose, less numerous eosinophils, lymphocytes, plasma cells, mast cells and muscle fibres can be seen. Proliferative changes or squamous metaplasia can be seen in the overlying epithelium. Our findings were in concordance to these findings described in literature. Many recent studies have found association of EC with findings like Charcot laden crystals [13], lupus anticoagulant and celiac disease. No such associations were seen in this study.

Antiphosphospholipid antibodies, BK virus infection of bladder and hemorrhagic cystitis may play a role in generation of EC or may be secondary to the tissue damage occurring in EC. Recently, Enterobacter & Proteus mirabilis have been found to be associated with EC. In various studies it has been observed that EC can be associated with repeated bacterial urinary tract infections, prostate hyperplasia, bladder stones, prostate or bladder surgery or medications. Development of EC in most cases of urothelial carcinoma post chemotherapy has also been noted [3,13]. The patients with EC can present with various complications [14,15], most common being unilateral or bilateral hydroureteronephrosis (HUN), due to inflammation obstructing the intramural ureter. Two patients in the present study presented with HUN. Other complications which can occur are eosinophilic ureteritis, eosinophilic cholangitis, retroperitoneal fibrosis, spontaneous bladder perforation with persistent vesical fistula and vesicoureteral reflux.

The first step in the management of EC is to identify and remove the precipitating agents. In cases which lack any inciting factor, urinalysis and culture should be done along with cystoscopy and biopsy. The first line drugs which can be used are Non-steroidal anti-inflammatory agents and antihistamines. Corticosteroids, cyclosporine, antibiotics and doxorubicin have also been used. Electrocoagulation, endoscopic resection of bladder mass, partial cystectomy, radical cystectomy with reconstruction or prostatectomy have been done in refractory cases. (2,14,15) The most common treatment modality used in our study population was a course of antibiotics which was found effective in alleviating the urinary symptoms.

**Conclusion**

Eosinophilic cystitis is an important, infrequent condition seen in patients evaluated for various genitourinary tract symptoms and may mimic a bladder tumor. It is important to

investigate for associated genitourinary conditions in all patients diagnosed with EC inorder to provide prompt treatment. Hence, a proper clinico-pathological and radiological assessment helps in accurate diagnosis of EC and to detect any associated conditions like malignancy or BPH.

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