CASE REPORT

# Eosinophilic cystitis: three cases, and a review over 10 years

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## SUMMARY

Eosinophilic cystitis (EC) is a rare disease. We describe three cases, where presentations of the disease are similar. To highlight probable causes of the disease, symptoms, clinical findings and treatment modalities, we reviewed 56 cases over a 10-year period. The most common symptoms were frequency, dysuria, urgency, pain and haematuria. Common clinical findings were presence of bladder mass, peripheral eosinophilia and thickened bladder wall. A variety of medical treatments were used, most frequently steroids, antibiotics and antihistamines. Recurrence occurred in patients on tapering or discontinuing prednisone, among other reasons. There is no consensus about the treatment of EC, but In light of our findings in this review, the treatment of choice in our department will be tapered prednisone over 6–8 weeks in combination with antihistamine.

## BACKGROUND

Eosinophilic cystitis (EC) is a rare bladder disease first described by Edwin Brown in 1960.[1] Histological findings include transmural inflammation of the bladder, predominantly with eosinophil. In the chronic stage, fibrosis and muscle necrosis may also be seen which may lead to contracted bladder.[2 3]

The cause and pathogenesis of the disease is unclear, and not fully understood. It is speculated that an antigen–antibody complex is formed on antigen exposure in the bladder. This IgE-mediated response leads to degranulation of mast cells, thereby attracting eosinophil and causing an inflammatory response with tissue damage.[4 5] Many aetiologies and associations to other diseases have been proposed.[3 5] These include different medications, vesical injury, chronic vesical irritation, subsequent to vesical surgery, parasitosis, allergy to food and drugs, urinary tract infection (UTI), urothelial carcinoma, autoimmune disorders and eosinophilic enteritis.[5 6]

EC is described in all age groups,[2] although to a lesser degree in the paediatric population.[4] The condition usually causes irritative bladder symptoms, suprapubic pain and haematuria.[3] In some cases the findings may simulate UTI or on radiological imaging and cystoscopy, mimic a malignant lesion.[6 7]

It is important to focus on this rare disease, as the variable symptomatic and clinical presentation of EC may lead to delayed diagnosis and treatment. In turn, delayed or insufficient treatment of EC can lead to increased discomfort for the patient due to the potential chronicity of the condition, as well as recurrence of symptoms.

## CASE PRESENTATION

### Case 1

A 14-year-old boy with a medical history of type 1 diabetes, asthmatic bronchitis and allergies, was referred to paediatric outpatient evaluation due to 2 weeks persistent microscopic haematuria, dysuria, frequency and one event of painful terminal gross haematuria. Urine cultures were performed twice during the 2-week period, both negative. Physical examination was unremarkable. Urinalysis revealed pyuria and haematuria. Repeated urine culture was negative.

The patient was referred to our department. CT urography and blood analysis were normal. A flexible cystoscopy revealed hyperaemia of the whole bladder mucosa with no signs of bladder mass. Fluorescence cystoscopy with biopsies was performed 3 weeks later, and findings at this time were discreet. Postoperatively the patient was treated for suspected UTI due to recurrence of symptoms, but urine culture was negative. Histopathology was consistent with EC, showing severe subepithelial inflammatory changes with predominance of eosinophil (figure 1). The patient was evaluated at a specialist department. At this time, 2 months after biopsies were taken, the patient was asymptomatic. Owing to the patient's diabetes, and him being asymptomatic, no treatment was initiated. The patient remains asymptomatic 5 months after the biopsies revealed EC, and is scheduled for follow-up in 1 year.

### Case 2

A 78-year-old man was referred to our department due to gross haematuria, frequency and dysuria throughout 2 months. His medical history included hypertension, nephropathy and coronary bypass. CT scan revealed thickened bladder wall (figure 2). Urinalysis showed pyuria, haematuria and proteinuria and the patient was treated for suspected UTI. Subsequent urine culture was negative. Cystoscopy revealed oedematous, hyperaemic bladder mucosa suspicious of carcinoma *in situ*. Biopsies showed severely inflamed bladder mucosa and benign lymphoid follicles and eosinophilia infiltration (figure 3). The patient was treated with prednisone 37.5 mg per day for 10 days. Haematuria subsided and frequency at daytime improved, although the patient still reported frequent urination during the night. Urine culture was still negative.

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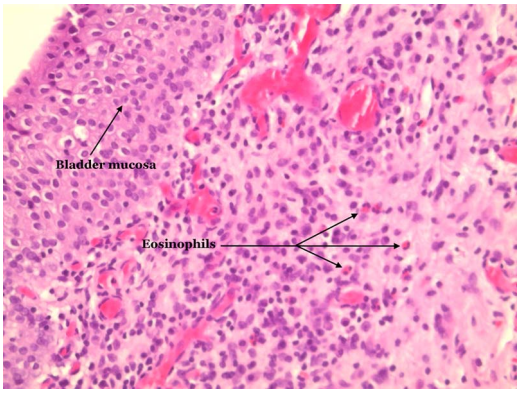


**Figure 1** Bladder biopsy with inflammation in the lamina propria. Several eosinophilic granulocytes, with red granules in the cytoplasm and two nuclear segments (H&E ×20).

Two and a half months later, the patient experienced gross haematuria. Urinalysis was still positive for erythrocytes, white cell count and protein. Treatment with prednisone for 10 days was initiated.

Three months later, the patient experienced symptom recurrence again. CT revealed sustained thickening of the bladder wall, and at cystoscopy, biopsies were taken from an erythematous plaque. Histopathology was consistent with EC. The patient's symptoms resolved without medical treatment and the patient is scheduled for follow-up in 6 months.

### Case 3

A 83-year-old man was admitted to our department due to gross haematuria and urinary retention. His medical history included hypertension, atrial fibrillation and benign prostatic hypertrophy. Urinalysis revealed pyuria, haematuria and positive nitrite. He was treated with antibiotics and insertion of indwelling bladder catheter. CT urography showed benign, bilateral kidney cysts. Cystoscopy revealed vulnerable, erythematous bladder mucosa and a bladder mass. The bladder mass was resected and biopsies from bladder mucosa were obtained. Histological findings were acute and chronic inflammation, granulation tissue, eosinophilia and fibrosis. The patient's symptoms resolved after surgery. Twenty-three months later the patient had recurrence of gross haematuria and cystoscopy findings were normal apart from some bleeding from the prostate. Treatment with prednisone was not considered.

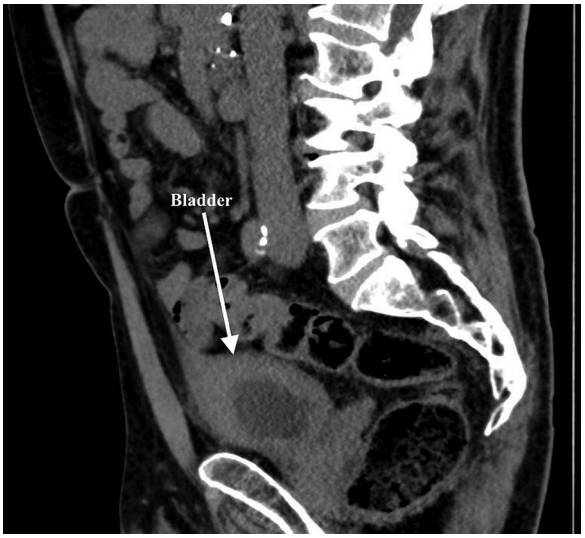


**Figure 2** CT scan with sagittal section, an arrow shows thickened bladder wall.

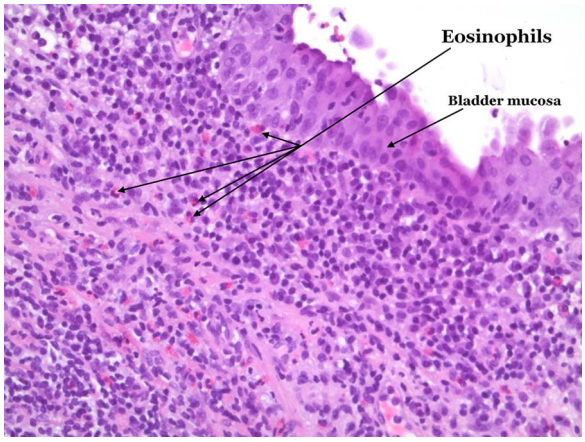


**Figure 3** Bladder biopsy; inflammation with eosinophilic granulocytes in the lamina propria (H&E ×20).

## INVESTIGATIONS

*Case 1*
CT urography: normal
Blood analysis: normal.
Urinalysis: pyuria, haematuria, negative culture.
Cystoscopy: hyperaemia of bladder mucosa.
*Case 2*
CT scan: thickened bladder wall.
Blood analysis: normal.
Urinalysis: pyuria, proteinuria, haematuria, negative culture.
Cystoscopy: oedematous, hyperaemic bladder mucosa.
*Case 3*
CT urography: benign kidney cysts.
Blood analysis: marginally elevated creatinine (1.22 mg/dL) and slight anaemia (haemoglobin 7.8 mmol/L). Creatinine levels normalised after surgery, and haemoglobin reached normal levels 1 month postsurgery.
Urinalysis: haematuria. Five months later: pyuria, haematuria and positive nitrite, positive urine culture (at this time the patient had indwelling catheter).
Cystoscopy: erythema, bladder mass.

## DIFFERENTIAL DIAGNOSIS

- Interstitial cystitis
- Carcinoma in situ (CIS)
- Haemorrhagic cystitis
- Bladder cancer
- Lower urinary track symptoms (LUTS)

## TREATMENT

Case 1: Owing to the patient's diabetes and asymptomatic feature of EC, prednisone treatment was not initiated.
Case 2: Two courses of prednisone 37.5 mg for 10 days.
Case 3: Resection of bladder mass.

## OUTCOME AND FOLLOW-UP

Case 1: Symptoms recurred after surgery, but subsided once again, spontaneously. The patient remains asymptomatic

**Table 1** Common symptoms in EC

| Symptom | N |
|---|---|
| Frequency, dysuria, urgency, pain on bladder filling[2 4 7–28] | 33 (59%) |
| Pain (abdominal/pelvic/suprapubic/groin/flank/hypogastric)[4 7 8 10–13 15–17 19 20 22 25 27 29–31] | 21 (38%) |
| Urine retention[4 13 16 20 31 32] | 6 (11%) |

**Table 3** Possible causes and associations of EC to other diseases

| Causes/associations | N |
|---|---|
| History of—or family history of asthma/allergy/atopy, family history and/or positive skintest[2 4 10 11 13 18 20 22 25 31 35] | 15 (27%) |
| Bacterial infection[4 11 13 16 18 20 32] | 9 (16%) |
| Medically induced[2 4 13 15 25 31] | 7 (13%) |

EC, eosinophilic cystitis

5 months after bladder biopsies and a 1-year follow-up is scheduled.

Case 2: The patient was treated with prednisone 37.5 mg/day after surgery. At recurrence 3 months later, a new course of prednisolone initiated. At second recurrence bladder lesions were biopsied, and the patient's symptoms resolved with no further treatment. Follow-up is scheduled within 6 months.

Case 3: The patient became asymptomatic after resection of bladder mass. At recurrence of haematuria, there was no evidence of EC relapse.

## DISCUSSION

We performed a literature search in PubMed from 2003 to 2013 using the search word 'eosinophilic cystitis', 'eosinophilic AND bladder'. The search generated 62 items. Of these, 30 were not of relevance on the topic or were not English. The remaining 32 articles included 56 cases of EC.

The most common symptoms and clinical findings of EC are listed in tables 1 and 2 respectively.

In the majority of cases, there was no obvious cause for EC. Some cases of EC were most likely caused by medication (penicillin,[25] Coumadin,[13] BCG,[15] levetiracetam,[4] dimethyl sulfoxide and Mitomycin-C[2 13]). The most common causative and associative factors to EC are listed in table 3. Less common possible causes of EC were mononucleosis,[20] recurrent UTI,[20 32] chronic granulomatous disease,[23] BK polyoma virus infection,[13] blood cord transfusion,[14] bladder stones,[2 13] previous pelvic trauma,[19] nephrogenic adenoma,[29] parasitic infection[8 32] and hypereosinophilic syndrome.[7 12 27]

**Table 2** Clinical findings in EC

| Finding | N |
|---|---|
| Haematuria (gross, microscopic)[2 4 7 9–21 23 24 27 32–35] | 28 (50%) |
| Bladder mass/velvety lesions[2 4 7 9 10 13 15 16 18 20 23 28 29 33 35 36] | 27 (48%) |
| Peripheral eosinophilia[4 7 9 11 12 15 16 18 20 22 25–27 31 33 34] | 21 (38%) |
| Thickened bladder wall[2 4 7 9 10 13 15 16 18 20 23 28 29 33 35 36] | 21 (38%) |
| Haemorrhagic lesions/erythema/ulcers/erythematous plaques[8 10 14 19 20 24 27 32 34 36] | 16 (29%) |
| Oedema/inflammation of the bladder mucosa[2 4 9 11 12 14 17–20 25 27 34] | 15 (27%) |
| Hydronephrosis/hydroureteronephrosis[2 4 11 15 16 29 32 33] | 11 (20%) |
| Pyuria[4 9 11 12 16 18 23 28 34] | 10 (18%) |
| Positive urine culture[4 11 13 16 18 20 32] | 9 (16%) |
| Reduced bladder capacity/compliance[4 25 28] | 3 (5%) |
| Vesicoureteral reflux[4 17 29] | 3 (5%) |
| Inflammation of the ureter/pelvis/ureteral orifice[17 31] | 2 (4%) |
| Paracytosis[8 32] | 2 (4%) |
| Stenosis of the ureteral orifice[29] | 1 (2%) |
| Bladder neck contracture[13] | 1 (2%) |
| Abdominal distention (free fluid in abdomen)[30] | 1 (2%) |

Owing to the rarity of EC, treatment is not standardised and treatment modalities as well as course of treatment varied throughout cases (table 4). Steroids were most commonly used, but 21% of patients treated with steroids either had no relief of symptoms or symptoms recurred during or after treatment. Of these patients, three underwent surgical treatment,[17 20 29] one patient received a longer treatment with steroids at recurrence,[24] and one was started on ciclosporin combined with antihistamine.[23] Finally, a parasitic infection was detected in one patient who was then treated accordingly.[8] The most common combination of medications used, were antihistamines with steroids.[2 10 11 16 23 27 31 33] Twelve patients (21%) underwent surgery as the only treatment.[2 13 30 35 36]

Sixteen per cent of patients had recurrence of symptoms either during or after primary treatment. In two patients, recurrence of symptoms occurred while tapering prednisone.[7 23] Two patients had relapse of symptoms after discontinuing prednisone,[24 27] and steroid treatment was reinitiated. Symptoms recurred in one patient after ended prednisone treatment while tapering montelucast,[18] and in another while tapering antihistamine.[28] One patient, where resection of EC lesions was performed without further medical treatment, had recurrence of symptoms 1 year postoperatively and was treated with prednisone causing symptoms to resolve.[2] Two patients had debilitating cases of EC, where no medical treatment led to persistent resolution of symptoms, which prompted surgical intervention with cystoureterectomy[17] and partial cystectomy.[20]

**Table 4** Treatments for EC

| Treatment | N |
|---|---|
| Steroids[2 4 7–12 14–19 22–24 26 27 29 31 33 34] | 29 (52%) |
| Antibiotics (treatment or prophylactic)[4 9 11–13 16 18 20 26 28 32] | 14 (25%) |
| Antihistamine[2 10 11 16 20 23 27 28 31–33] | 14 (25%) |
| Surgery (excluding bladder biopsies/resection of bladder lesions)[2 13 17 19–21] | 8 (14%) |
| NSAID[7 10 20 33] | 5 (9%) |
| No treatment[13 25] | 4 (7%) |
| Antiparasitic medication[8 28 32] | 3 (5%) |
| Montelucast[8 18] | 2 (4%) |
| Infravesical sodium pentosan polysulfate[17 31] | 2 (4%) |
| Spasmolytic[10 13] | 2 (4%) |
| Infravesical steroid[17 32] | 2 (4%) |
| α-receptor blocker[25 27] | 2 (4%) |
| TUR-B[15 16] | 2 (4%) |
| Gabapentine[31] | 1 (2%) |
| Nephrostomy[15] | 1 (2%) |
| Ciclosporin[23] | 1 (2%) |
| Sodium chromoglycate[7] | 1 (2%) |
| Suplatast tosilate (cytokine inhibitor)[9] | 1 (2%) |

NSAID, non-steroidal anti-inflammatory drug.

Of the cases with symptom recurrence, the most obvious cause was insufficient treatment with steroids (early treatment interruption or tapering). In light of this, as well as our experience with recurrence after short-term treatment with prednisone (case 2), the treatment of choice at our institution, will be removal of the suspected causative factor to the disease combined with long-term tapered prednisone (6–8 weeks) and antihistamine. To ensure timely treatment modification in cases of EC treatment failure and recurrence, we have now set up a scheduled follow-up regimen for patients diagnosed with EC in our department. In cases where patients become symptom-free after resection of EC lesions, medical treatment is not initiated, and patients are reassessed after 1 year. In cases where medical treatment is initiated, treatment evaluation is performed after 2 weeks. If symptoms are improving the patients are evaluated again after 4 weeks and at treatment completion where flexible cystoscopy is performed to ensure that lesions have fully regressed. If symptoms have not improved, or are worsening at first follow-up, flexible cystoscopy is performed. In cases where lesions are found, prednisone dosage is altered and re-evaluation of treatment efficacy is planned after 1–2 weeks. Hereafter, individual future evaluation is planned depending on symptoms and clinical findings.

At recurrence, or in cases where systemic steroids are relatively contraindicated (case 1), bladder instillation with steroids may become a treatment option. In refractory cases, surgery may be the only curative treatment.

## Learning points

- Eosinophilic cystitis (EC) is a rare disease with transmural infiltration of eosinophil.
- Diagnosis of EC is histopathological.
- Patients with EC often have symptoms and clinical findings common to other urological disorders, such as urinary tract infection, malignancy and lower urinary symptoms.
- No standardised treatment exists, but common, effective treatments include steroids, antihistamines, and surgery—often in combination.

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