

SHORT REPORT

Eosinophilic cystitis

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Abstract

We describe four cases of eosinophilic cystitis in whom no specific cause could be found, and review the literature. Complaints at presentation included urgency, frequency, abdominal pain, and haematuria. In three patients the symptoms and ultrasound pictures suggested a bladder tumour. One patient was treated with anticholinergics and corticosteroids without relief of symptoms; a localised eosinophilic tumour was excised in one patient who remained symptom free; and two patients were managed conservatively with spontaneous resolution of bladder pathology and symptoms. One case was identified by random bladder biopsy in 150 consecutive patients with unexplained irritable micturition complaints. Eosinophilic cystitis is rare in children. After biopsy, we consider a wait and see policy is justified as symptoms tend to disappear spontaneously. Routine bladder biopsies in children with unexplained bladder symptoms is not justifiable.

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The aetiology and treatment of eosinophilic cystitis remain poorly understood in spite of many case reports. Brown is often quoted as the first to publish on eosinophilic cystitis owing to his description of eosinophilic granulomas of the bladder wall.¹ In 1949 Kindall and Nickels identified eosinophilic leucocytes in the urine and in the bladder wall of patients with micturition complaints. These patients improved after eliminating suspected food allergens from their diet.²

The pertinent characteristic of the disease is eosinophilic infiltration as observed in bladder wall biopsy specimens. The symptoms often mimic those of urinary tract infection. The bladder lesions seen by ultrasound and cystoscopy may be initially interpreted as malignant.

Several drugs have been reported to induce eosinophilic cystitis in adults: cyclophosphamide,³ coumadin,⁴ tranilast (an antiallergic drug),⁵ penicillin, and clometacin.⁶ Intravesical instillations with mitomycin and thiotepa can cause eosinophilic infiltration of the bladder wall.⁷⁻⁸ Goble *et al* found urothelial eosinophilic infiltration in response to catheterisation.⁹ Engler *et al* reported eosinophilic cystitis at the site of chromic catgut sutures.¹⁰

Treatment is empirical.¹¹ It consists of removal of any suspected allergen. Corticosteroids, anticholinergic drugs, and antiallergic drugs have been reported to relieve symptoms. Partial cystectomy has been performed in cases of circumscribed lesions that show no tendency to disappear spontaneously.¹² Many reports mention the self limiting course of the disease.¹³⁻²⁸ Our search of the literature produced 24 patients under the age of 18 (table 1). Seventeen presented with a tumour in the bladder. The symptoms subsided spontaneously or during corticosteroid therapy in 20, including 15 with a bladder mass.

Our study comprises four children with eosinophilic cystitis. Three were suspected of having bladder tumours. One was identified by our previous policy to perform bladder biopsies in children with severe unexplained micturition complaints. We assessed retrospectively how often eosinophilic cystitis was found in this group of 150 consecutive patients.

Patients and results

One patient (patient A) was identified on routine bladder biopsies in patients with unexplained micturition complaints. No specific pathological diagnosis was established in the 149 other patients biopsied. The symptoms of

Table 1 Literature review

First author	Year of publication	Sex	Age (y)	Tumour	Therapy	Time for symptoms to subside (wk)
Farber ¹³	63	F	3	+	Stibophen	28
Wenzl ²⁹	64	F	6	-	Antibiotics	Exacerbations > 8 months
Champion ¹⁴	66	F	2	-	Antibiotics	2
		M	12	+	Antibiotics	8
Perlmutter ³⁰	68	M	8	+	Resection	Uneventful recovery
Kessler ¹⁵	75	F	0*	+	Steroids	2
Tauscher ¹⁶	81	M	3	+	None	10
Aubert ¹⁷	83	M	17	-	Imuran	6
Snow ¹⁸	84	M	4	+	Steroids	1
Sutphin ¹⁹	84	M	7	+	None	6
Peterson ²⁰	85	M	1	-	Steroids	3
Axelrod ²¹	91	F	7	+	Steroids	2
Bauer ²²	91	M	2	+	Antibiotics	4
		M	5	+	None	Granulomatous infiltration lung
Sujka ²³	92	M	14	-	Antibiotics	4
Spark ³¹	91	M	3	-	Resection	Ureteritis; uneventful recovery
Gerharz ²⁴	94	M	11	+	Steroids	2
Vetter ³²	95	F	2	+	Resection	Uneventful recovery
Ladocsi ²⁵	95	M	4	+	Steroids	12
		F	5	+	Steroids	2
		M	3	-	None	Intermittent symptoms > 1 year
Scully ²⁶	98	F	10	+	Steroids	<1
Netto ²⁷	99	M	11	+	TUR	4
		F	2	+	Drainage	8

*Five days.

TUR, transurethral resection.

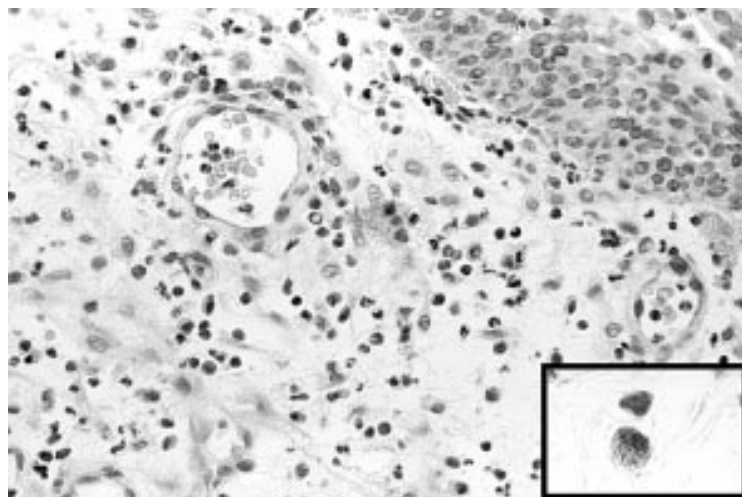


Figure 1 Bladder biopsy of patient D, showing an inflammatory infiltrate of the subepithelial connective tissue, predominantly composed of eosinophilic leucocytes. Inset: detail.

patient A were not remarkably different from the other biopsied patients. Our other three patients (B, C, and D) were referred because of pain and/or haematuria. The clinical suspicion of a bladder tumour leads to the diagnosis.

Patient A, a boy, became continent night and day at 3.5 years of age. At 4 he started wetting day and night, for which he was evaluated elsewhere. Both parents had suffered nocturnal enuresis until the age of 14. At 9 years of age he became dry during the day, taking oxyphenonium bromide 5 mg three times daily and imipramine chloride 25 mg twice daily. Physical examination and laboratory results were normal except for a modest blood eosinophilia ($0.5 \times 10^9/l$). A grade 2 reflux was found at the right hand side on the micturition cystogram. Intravenous urography was normal. He presented to our department at the age of 11 because of persistent nocturnal enuresis and frequency. He was of normal height and weight. Blood pressure was 90/60 mm Hg. White blood cell count (WBC) showed 8.1×10^9 leucocytes/l with 1.5×10^9 eosinophils/l. Repeated urine sediments and cultures were normal. Analysis of stools revealed no cysts or worm eggs. Allergic tests were positive for dust mite, pollen, canary, parrot, and parakeet. Serum IgE was 2200 IU/ml (normal <100 IU/ml). Cystoscopic examination showed a hyperaemic mucosa. Random biopsy specimens showed eosinophilic infiltration of the bladder wall. Oxyphenonium bromide was continued. He did not improve over six months follow up.

Patient B is a 17 year old girl. At the age of 5 bilateral kidney hypoplasia was diagnosed. Renal function had decreased progressively. At the age of 16 an arteriovenous shunt was constructed for renal dialysis. Shortly after, she presented at the urologic department because of pain in the left groin at micturition. Voiding frequency was eight to 10 times during the day and two to three times during the night. She was on the following medication: aluminium hydroxide 0.5 g twice daily; sodium bicarbonate 1 g four times daily; calcium 500 mg three

times daily; dihydrotachysterol 0.2 mg twice daily; dipyridamol 25 mg twice daily; dagravit 30 (multivitamin) one tablet daily; lynestrenol (oral contraceptive) 0.5 mg once daily; and acenocoumarol according to INR. Her dietary protein was restricted to 40 g per day. On physical examination we found her height on the 5th centile with normal weight for height. Blood pressure was 107/54 mm Hg. Rectal and vaginal examination revealed a spherical tumour of 5 cm diameter on the left side fixed to the pelvis. Results of laboratory investigations were as follows: erythrocyte sedimentation rate (ESR) 108 mm/h; WBC $8.3 \times 10^9/l$; eosinophilic leucocytes $0.17 \times 10^9/l$; haemoglobin 5.8 mmol/l; haematocrit 0.29; urea 27 mmol/l; and creatinine 990 μ mol/l. The urine sediment contained more than 40 leucocytes and more than 40 erythrocytes per high power field. Urine cultures were repeatedly negative (24 hour urine: volume 2.1 l; Na 77 mmol/l; K 15 mmol/l; urea 67 mmol/l; creatinine 3.2 mmol/l). Amino acid excretion was high for branched amino acids, iminoacids, citrulline, and arginine (Fanconi syndrome). Abdominal ultrasound showed a 45 mm tumour which was continuous with the bladder wall. At cystoscopy, this was seen protruding into the bladder. Biopsy specimens showed severe infiltration with eosinophilic leucocytes. The tumour was removed by laparotomy and partial cystectomy. The sigmoid colon was adherent to the tumour. Histological analysis showed homogeneous eosinophilic infiltration throughout the swelling. The patient was free of urological symptoms after this procedure and has remained so for 10 years.

Patient C, an 11 year old boy, was referred to our department because of terminal haematuria and pain during micturition. His voiding frequency had increased from four to eight times daily. On physical examination he was of normal height with weight for height according to the 75th centile. His blood pressure was 113/58 mm Hg. Abdominal investigation revealed a slight suprapubic pain. Results of laboratory investigations were as follows: ESR 3 mm/h; haemoglobin 9.2 mmol/l; WBC $9.5 \times 10^9/l$; eosinophilic leucocytes were within normal range. Urine sediment contained one to five leucocytes per high power field. Urine cultures were negative. Stools showed no cysts or worm eggs. An abdominal ultrasound showed normal kidneys. The bladder contained an irregular mass, suspected to be malignant. Cystoscopy showed severe oedema of the bladder neck. Biopsy specimens taken from the oedematous area showed submucosal eosinophilic infiltration. Symptoms resolved spontaneously over several days.

Patient D, an 11 year old girl, was referred because of urgency and haematuria. She was allergic to pollen and used ketotifen, discontinued shortly before referral. Rectal examination revealed a mobile 3 cm diameter pelvic mass. Results of laboratory investigations were as follows: WBC $7.3 \times 10^9/l$; eosinophilic leucocytes $0.07 \times 10^9/l$, serum IgE 73 IU/ml (normal). Abdominal ultrasound showed an irregular tumour in the bladder. Transurethral bladder

biopsy specimens of the tumour showed infiltration of the bladder wall by eosinophils (fig 1). Spontaneous resolution of symptoms occurred over several days. After three months the tumour had disappeared.

Discussion

Eosinophilic cystitis has a variable presentation and outcome. Two of our four patients were known to have allergies, an association also reported in the literature (five of 24 reported paediatric patients had allergies). However, we could not identify a cause of the disease in our patients. Patient D had used ketotifen which was discontinued shortly before the diagnosis of eosinophilic cystitis. Ketotifen has not been reported to induce eosinophilic cystitis but a variety of different compounds are believed to cause this.³⁻⁸ Eosinophilic cystitis may clinically resemble a bladder tumour. Development of a secondary malignancy has never been reported. On the contrary, as in our cases, a self limiting course in children is often observed.¹³⁻²⁷ Patient A is our only patient whose symptoms did not resolve spontaneously, possibly due to limited follow up. In retrospect, it is possible that resolution in patient B might have also been accomplished by more conservative management.

In children with unexplained micturition complaints, eosinophilic cystitis is rarely found. In our patients no other explanation for the micturition complaints was revealed by the bladder biopsies. We conclude that routine bladder biopsy in children with unexplained urgency is not justifiable.

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