

# Eosinophilic Cystitis in a 4-Year-Old Boy: Successful Long-Term Treatment With Cyclosporin A

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**ABSTRACT.** A 4-year-old Jewish boy presented with dysuria, urinary dribbling, increased urinary frequency, and new onset of diurnal enuresis. An infiltrating solid mass involving the entire bladder wall was found. Biopsy revealed "tumor-forming" eosinophilic cystitis, a rare bladder lesion of unclear cause. Antitoxocariasis treatment was unsuccessful. High-dose corticosteroids failed. The child's clinical condition and bladder sonographic findings continued to deteriorate. Treatment with cyclosporin A was given for 8 months, with a complete clinical, radiologic, and histopathologic cure and no side effects. Two years of follow-up showed a complete recovery. *Pediatrics* 2001;108(6). URL: <http://www.pediatrics.org/cgi/content/full/108/6/e113>; *cystitis, eosinophilic, cyclosporin A*.

Eosinophilic cystitis is a rare disorder of the urinary bladder, characterized by extensive local eosinophilic infiltration of all layers of the bladder wall, probably induced by a regulatory disorder of the immune system. Many possible causes have been postulated; nevertheless, the exact mechanism of the disease still needs to be clarified. This uncommon entity was first reported almost 40 years ago<sup>1,2</sup> and can be encountered in any age group, although it seems to be more common in adults. Eosinophilic cystitis has a broad spectrum of clinical and pathologic manifestations, ranging from mild inflammatory cystitis to severe chronic or recurrent relentless inflammation.<sup>3–8</sup> This disorder eventually can progress to a complete fibrosis of the urinary bladder with secondary involvement of the rest of the urinary tract, resulting in obstructive nephropathy with variable degrees of renal insufficiency.<sup>3–9</sup> We report a child who had severe progressive eosinophilic cystitis and did not respond to high-dose corticosteroid therapy and specific therapy for toxocariasis. Repeated bladder sonography suggested progressive reduction of the urinary bladder lumen with extensive fibrosis of the bladder wall. Long-term treatment with cyclosporin A resulted in clinical recovery with complete disappearance of the bladder eosinophilic infiltration.

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Received for publication May 14, 2001; accepted Aug 14, 2001.

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## CASE REPORT

A 4-year-old Jewish boy, who was born to a healthy mother of Turkish origin and a Moroccan father, had received a diagnosis of celiac disease. His 6-year-old sister was healthy. The patient was a term infant, appropriate for gestational age, and born after an uneventful pregnancy and delivery. Growth and development were normal. At age 1.5 years, he underwent a left orchidopexy for an undescended testis.

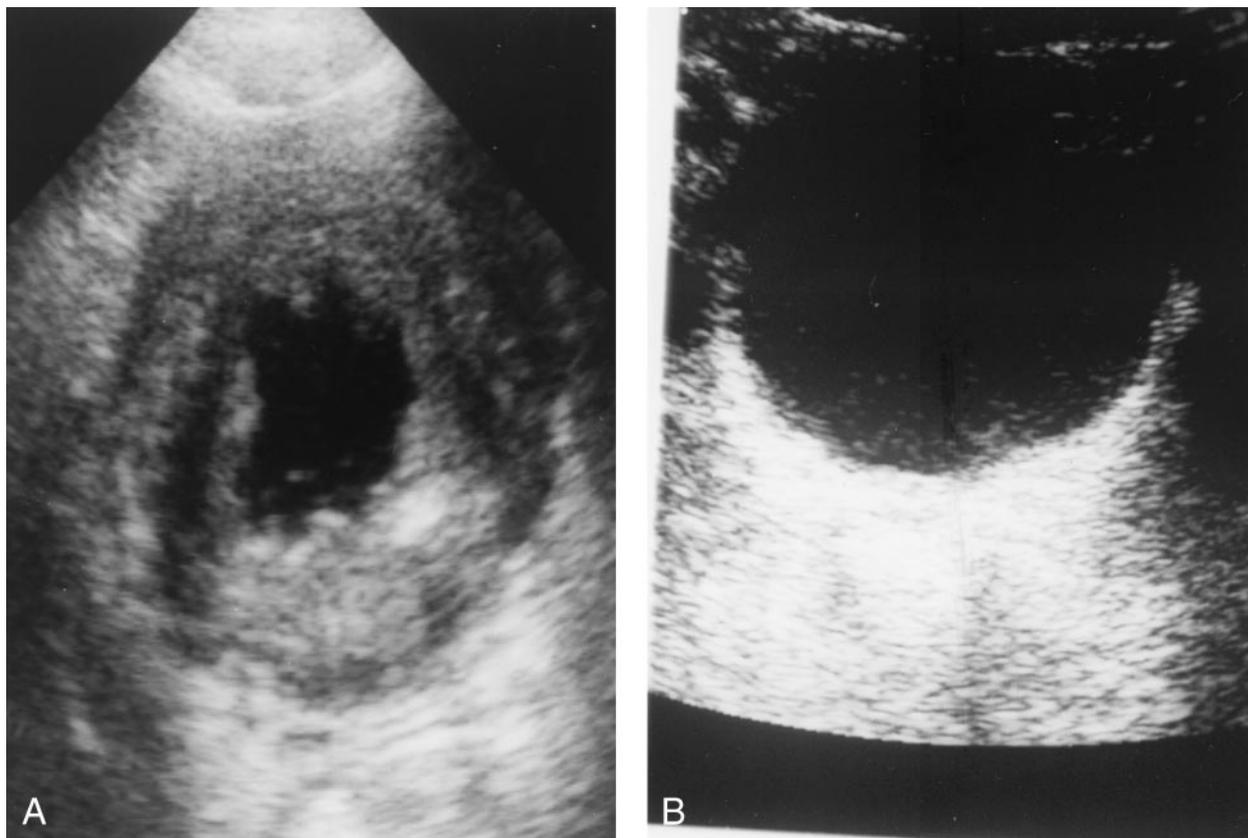
He presented with a 2.5-month history of dysuria, urinary frequency and urgency, dribbling, and diurnal enuresis. Body temperature was normal. No abnormalities were detected in the physical examination. The laboratory results showed a white cell count of 12 000/ $\mu$ L with 32% neutrophils, 60% lymphocytes, 6% monocytes, and 2% eosinophils.

Hemoglobin was 11.8 g/dL, and the red blood cell count was  $4.54 \times 10^6/\mu$ L, with normal indices. Platelet count, erythrocyte sedimentation rate, and liver and kidney function tests were normal. Lactodehydrogenase level was elevated: 737 U/L (normal: 230–460 U/L). Antiendomysial and antigliadin antibodies were negative. Urinalysis was normal, and the urine creatinine-calcium ratio was 0.16 (normal). Repeated urine cultures were negative.

Renal sonogram revealed normal location, size, shape, and echogenicity of both kidneys, with normal parenchyma and corticomedullary ratio. There was no evidence of hydronephrosis. The bladder demonstrated concentric thickening of the wall and seemed to have a significantly reduced capacity (Fig 1A). Computed tomography confirmed the above findings (Fig 2A). Radionuclide scintigraphy (<sup>99m</sup>Tc–dimethyl succinic acid/dimethyl 3-penta-acetic acid) was normal. Voiding cystourethrography demonstrated significant reduction of bladder capacity. Transurethral cystoscopy disclosed a large mass above the ureteral orifices. Bladder biopsy demonstrated massive eosinophilic infiltration of all layers of the bladder wall from the submucosa to the serosa (Fig 3). Patchy areas of fibrosis in the muscular layer were seen, with no evidence of granulomas, macrophages, or parasites. Chest radiographs and echocardiography were normal. Five-unit protein purified derived test was negative. Serology for *Echinococcus granulosus* and schistosomiasis (performed by the National Center for Infectious Diseases, Atlanta, GA) was negative. Enzyme immunoassay for toxocariasis was also performed at the National Center for Infectious Diseases and was positive, with a titer of 1:128 (titer >1:32 is positive).

Immunologic studies were normal and included 790 mg/dL IgG, 166 mg/mL IgA, 107 mg/mL IgM, and 79 IU/mL IgE. IgG subclasses were normal. CH50, AP50, CD3, CD4, CD8, CD4/CD8 ratio, CD56+, CD3–, and CD19, as well as neutrophil chemotaxis, random migration, superoxide generation, and bactericidal activities, all were normal. Although interleukin-4 and -5 could not be assessed before therapy, levels were found within the normal range (<10 ng/mL) 2 and 6 months after the initiation of cyclosporin A treatment.

Initially, the child was treated for toxocariasis with 400 mg/day albendazole for 3 days. Simultaneously, a course of a high-dose oral prednisone was instituted (4 mg/kg/day); doses were gradually reduced over 3 months. Serology for toxocariasis was repeated, and a significant reduction of titers was detected (from 1:128 to 1:8–1:4 within 3 months). Despite the aggressive treatment, complaints of dysuria, frequency of urination, urgency, and diurnal enuresis persisted. Monthly renal sonography showed no improvement. Moreover, progression of the bladder wall thickening



**Fig 1.** A, Bladder sonogram demonstrated concentric thickening of the bladder wall that seemed to have significantly reduced bladder capacity. B, Bladder wall thickening, which improved to mild thickening 7 months later.

ing with a decreased bladder capacity was observed. Periodic renal function evaluation was normal.

A new therapeutic approach was started with oral cyclosporin A, 6 mg/kg/day, with periodic monitoring of serum drug levels (kept between 100 and 300 ng/mL), complete blood counts, and liver and renal functions. Clinical improvement was observed within 1 month. Diurnal enuresis, dysuria, and frequency disappeared after 2 months.

After 2 months of treatment with cyclosporin A, bladder ultrasound revealed moderate thickening of the bladder wall, which improved to mild thickening at 7 months; computed tomography confirmed the above findings (Figs 1B and 2B). Repeat cystoscopy was performed plus transurethral bladder biopsy, which demonstrated only a mild inflammatory lymphohistiocytic infiltration of the bladder wall with isolated eosinophils. No side effects of cyclosporin A treatment were observed. Therapy was stopped 8 months after initiation. One year after cessation of the therapy, the child had no clinical complaints. Bladder ultrasound and interleukin levels were normal.

### DISCUSSION

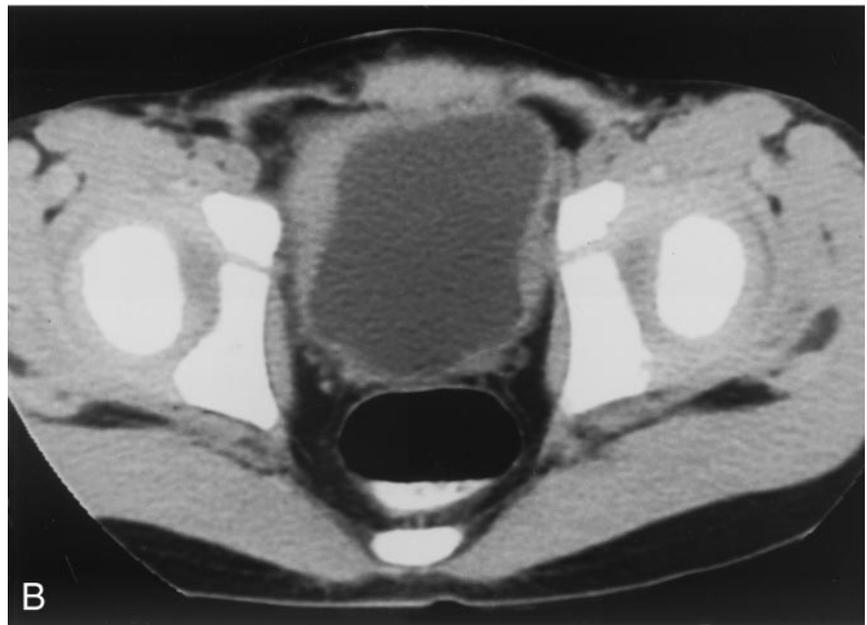
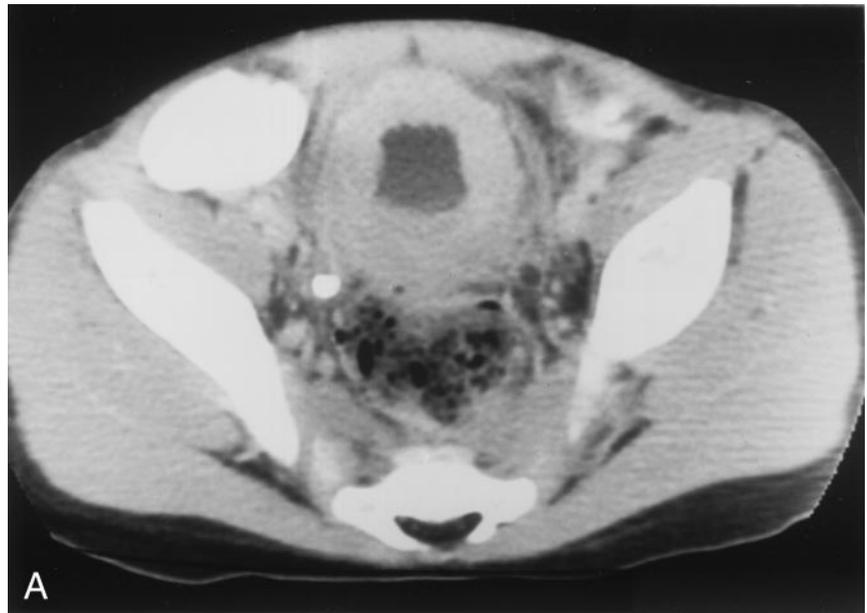
Eosinophilic cystitis is a rare inflammatory disorder of the urinary bladder and has an unclear cause. Several reports have been published since 1960<sup>1-8</sup> with only a few cases in children.<sup>10-16</sup> The disease has been reported in patients with a history of vesical injury and chronic vesical irritation, surgery,<sup>14,17</sup> parasitosis,<sup>11,18,19</sup> allergy to food and drugs,<sup>3,17,20-23</sup> tuberculous cystitis,<sup>24</sup> malignancies,<sup>25,26</sup> and other conditions.<sup>27-29</sup> Our patient had serology compatible with acute visceral larva migrans infection. Although serology reversed after specific treatment within 3 months, no clinical response was noticed. Moreover, deterioration of sonographic findings was apparent.

Long-term, high-dose corticosteroid treatment was ineffective. Usually, systemic visceral toxocariasis responds to medical treatment.<sup>30</sup>

Dysuria, frequency of urination, diurnal and nocturnal enuresis, suprapubic pain, and recurrent hematuria are usually the clinical and laboratory presentations of eosinophilic cystitis. Our patient presented with many clinical complaints but no urinary abnormalities. Hematuria, proteinuria, pyuria, and occasionally positive urine cultures are often found in eosinophilic cystitis. Peripheral blood eosinophilia can be present but not in the range of the hyper-eosinophilic syndrome. High serum levels of IgE have been reported but not in the range of the hyper-IgE syndrome. Urine cultures in our patient were normal, and peripheral eosinophilia and high serum levels of IgE were not present.

Imaging studies in patients with eosinophilic cystitis can mimic an infiltrating tumoral mass, as in our patient. It is imperative to obtain adequate deep biopsies; otherwise, the diagnosis can be missed. Initial transrectal and transurethral biopsies failed to obtain adequate tissue sampling; therefore, an open biopsy was performed.

The pathogenesis of eosinophilic cystitis is unclear; one suggestion (or hypothesis) is that a dysregulation of cytokines takes place (mainly interleukin-4 and -5). Cyclosporin A is a widely known immunoregulator, which may cause abnormal cytokine production.<sup>31</sup>



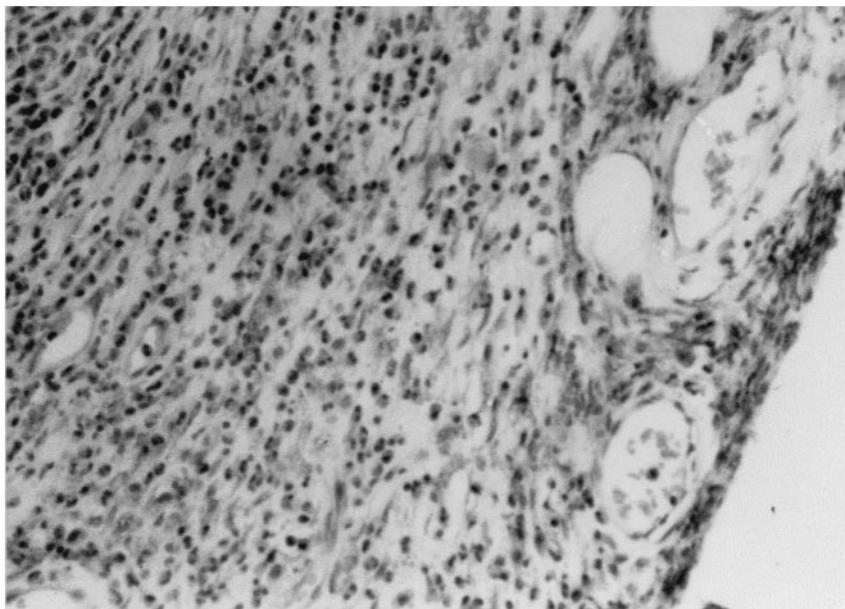
**Fig 2.** Computed tomography demonstrated concentric thickening of the bladder wall (A), which improved to mild thickening 7 months later (B).

Many treatments have been proposed, including radical surgery for advanced cases complicated by bladder fibrosis, which could endanger renal function. We believe that cyclosporin A should be considered a new possible treatment of eosinophilic cystitis.

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**Fig 3.** Eosinophilic infiltration with destruction of the muscularis of the bladder wall (hematoxylin-eosin,  $\times 400$ ).



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