

# The Spectrum of Eosinophilic Cystitis in Males

## Case Series and Literature Review

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● **Context.**—Eosinophilic cystitis (EC) is an inflammatory condition of the bladder that has been linked to food allergens, infectious agents, drugs, and other genitourinary conditions. Like interstitial cystitis, EC has a strong female predominance. It is characterized by an intense eosinophilic infiltrate in the acute phase and fibrosis in the chronic phase.

**Objectives.**—To document and focus on specific features of EC in males and highlight the relationship between clinical and histopathologic findings.

**Design.**—The bladder biopsies of male patients were reviewed. Eight cases of EC were selected.

Eosinophilic cystitis (EC) is an inflammatory condition first described more than 85 years ago.<sup>1</sup> Eosinophilic cystitis was regarded as a consequence of food allergens,<sup>1</sup> although other factors (inhalants, bacteria, viruses, and parasites) drew consideration.<sup>2-4</sup> Later, other allergenic agents were implicated such as condom antigens, contraceptive jellies, iodine, and anesthetic ointments.<sup>5</sup> Brown, in 1960, referred to the condition as *eosinophilic granuloma of the bladder* and asserted a relatedness to Hand-Schuler-Christian and Letterer-Siwe diseases.<sup>6</sup> With time other factors were proposed as putative initiators of EC, including parasitic infestation with *Toxocara cati*,<sup>7</sup> *Echinococcus granulosus*,<sup>8</sup> and *Sparganum*.<sup>9</sup> Extrapelvic infectious and inflammatory conditions were also noted: extensive skin infections with omphalitis,<sup>10</sup> infected urachal remnant,<sup>11</sup> and hypersensitivity to chromate catgut sutures.<sup>12</sup> A variety of medications including salicylazosulfapyridine, tranilast, Coumadin, and intravesical thiotepa and mitomycin were also implicated.<sup>13-17</sup> Finally, prostatic hyperplasia, and surgeries or tumors of the bladder and prostate were associated with EC.<sup>12,18-21</sup>

Eosinophilic cystitis has been reported at all ages (5 days to 87 years), 20% of cases occurring in children.<sup>21</sup> It shows a striking female predominance of 87%.<sup>4</sup> Other studies<sup>21,22</sup> showing equal sex incidence or slight male pre-

**Results.**—Several known associations were noted as well as unreported features and associations such as Charcot-Leyden crystals, celiac disease, lupus anticoagulant, and additional viral and bacterial agents.

**Conclusions.**—Eosinophilic cystitis represents a response to a variety of agents and may often be overlooked. The temporally biphasic morphologic features are the hallmark of this condition. Because clinical and imaging studies are not specific, a high index of clinical suspicion is often crucial to the correct diagnosis and proper management of EC.

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dominance reflect study group composition rather than actual incidence rates. Only one previous study has focused exclusively on male patients.<sup>23</sup> Eosinophilic cystitis in males has the same age distribution but appears to be related to different pathological genitourinary conditions and less associated with systemic or other organ conditions.<sup>7,17,19-21,23,24</sup> Clinical onset is commonly marked by urinary frequency, dysuria, gross hematuria, and suprapubic pain during micturition. Less frequent manifestations include microscopic hematuria, urinary retention, gastrointestinal symptoms (vomiting, diarrhea, tenesmus, bloody stool), urgency, incontinence, fever, skin rash, pneumaturia, and nocturnal enuresis.<sup>1-26</sup>

Urine cultures in EC are positive in some cases.<sup>6,15,20,24,27</sup> Cystoscopy findings are variable: ulcers, exudates, edematous bullae, or polyps (which may simulate malignancy).<sup>2-10,12-27</sup> Imaging studies (computed tomography scan, ultrasonography) may reveal thickening of the bladder wall and occasional mucosal polyps mimicking papillary tumors.<sup>28-32</sup>

Yamada and Taguchi<sup>33,34</sup> described the clinical features of 15 patients with contracted bladders. Four of their patients had distinct histopathologic changes in the bladder including a leukocytic infiltrate rich in lymphocytes, plasma cells, and eosinophils. The other 11 had renal tuberculosis and bladder lesions ascribed to mycobacterial infection. Although the authors did not indicate a threshold separating these groups, the inflammatory infiltrate, particularly the eosinophilia, was stressed. They regarded the first group as part of an interstitial cystitis phenomenon and discussed possible mechanisms of immune system dysregulation (autoimmunity, connective tissue disease, allergy, postinfectious antigenic cross-reactivity) and other factors that might be contributing factors.

The histopathologic features of EC may be classified as

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| Age of Patients, History, Clinical Symptoms, Associated Conditions, Endoscopic Imaging, Morphologic Features, Therapeutic Approach, and Outcome* |       |                                                                                                                                                                                                    |                                                                                                                                                                         |                                                                                 |
|--------------------------------------------------------------------------------------------------------------------------------------------------|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| Patient No.                                                                                                                                      | Age   | History                                                                                                                                                                                            | Symptoms or Associated Conditions                                                                                                                                       | Image by Endoscopy                                                              |
| 1                                                                                                                                                | 27 y  | Paraplegia (after MVA) UTI with <i>Klebsiella</i>                                                                                                                                                  | Hematuria, indwelling Foley catheter, Coumadin                                                                                                                          | Diffuse hemorrhagic edema of all bladder walls and deviation of the left ureter |
| 2                                                                                                                                                | 34 y  | Urothelial carcinoma, high grade of the bladder, instillations with mitomycin and thiotepa, bladder stones                                                                                         | NA (follow-up for carcinoma)                                                                                                                                            | NA                                                                              |
| 3                                                                                                                                                | 79 y  | Chronic indwelling Foley catheter, $\beta$ thalassemia trait, rectal carcinoma, transurethral resection of prostate                                                                                | Urinary retention, urethral voiding symptoms, frequency and urgency, lupus anticoagulant                                                                                | Erythematous bladder wall                                                       |
| 4                                                                                                                                                | 61 y  | Numerous episodes of irritable bladder symptoms (during 6 y), celiac sprue with a few exacerbations, prostatic hypertrophy                                                                         | Frequency, urgency, and pelvic/perineal pain                                                                                                                            | NA                                                                              |
| 5                                                                                                                                                | 52 y  | Negative for any medical or surgical history                                                                                                                                                       | Right ureteral calculus, persistent pain                                                                                                                                | Bladder neck contracture                                                        |
| 6                                                                                                                                                | 18 mo | Embryonal rhabdomyosarcoma of the prostate and bladder neck, UTI with <i>Klebsiella pneumoniae</i> and <i>Enterococcus</i>                                                                         | Fever and pancytopenia, febrile transfusion reaction (premedicated with an antihistaminic); urine culture positive for <i>Enterobacter</i> and <i>Proteus mirabilis</i> | Bladder neck mass (2.5 cm in the largest dimension)                             |
| 7                                                                                                                                                | 79 y  | Asthma, coronary artery disease, multiple UTIs positive for <i>Escherichia coli</i> , multiple upper respiratory infections, prostatic hypertrophy, postresection urothelial carcinoma, high grade | Decreased urinary stream                                                                                                                                                | Small papillary urothelial carcinoma                                            |
| 8                                                                                                                                                | 39 y  | Chronic myelogenous leukemia following allogeneic peripheral blood stem cell transplant                                                                                                            | Burning on urination, hematuria, BK virus infection                                                                                                                     | Numerous erythematous patches at the dome and the posterior bladder wall        |

\* MVA indicates motor vehicle accident; UTI, urinary tract infection; NA, not applicable; and EC, eosinophilic cystitis.

either “acute” or “chronic” phase.<sup>2-4,21,23</sup> The acute phase presents with tissue eosinophilia, mucosal edema and hyperemia, and muscle necrosis. In the chronic phase eosinophilia is not conspicuous, chronic inflammation is present to a variable degree, and scarring may be prominent. Early reports noted abundant eosinophils in 5% of the patients, these reflecting the early stage of disease.<sup>2-4</sup> Massive eosinophilic infiltrates are noted in areas adjacent to muscle necrosis (in the acute phase) but are absent in areas of muscle wall scarring (chronic phase). Mast cells and plasma cells may also be prominent in the chronic phase and squamous metaplasia and cystitis cystica have been reported.<sup>23</sup>

The biphasic nature of EC manifests the underlying mechanisms. In the acute phase antigen-antibody complexes attract eosinophils,<sup>35,36</sup> which release potent cationic proteins (such as urine eosinophil cationic protein) in high concentration that serve to enhance local inflammation and associated myonecrosis.<sup>37</sup> The acute phase of EC is triggered by a wide variety of injurious stimuli with resultant inflammation, oxidative stress, and creation of a cytokine-rich microenvironment, a potent recruiter of eosinophils and basophils.<sup>38-40</sup> In the wake of the intense proinflammatory storm of the acute phase, eosinophils secrete interleukins 5 and 12. These activate natural killer cells and T lymphocytes, favoring transition from a  $T_H2$  to a  $T_H1$  immune response<sup>41</sup> and the beginning of the chronic, smoldering phase of low-grade inflammation and fibrosis. The most frequent complication of EC is unilateral

or bilateral hydroureteronephrosis, possibly due to inflammation obstructing the intramural ureter. Less frequent complications include uremia,<sup>15</sup> eosinophilic ureteritis, eosinophilic cholangitis,<sup>42,43</sup> retroperitoneal fibrosis,<sup>44</sup> spontaneous bladder perforation with persistent vesical fistula,<sup>45</sup> and vesicoureteral reflux.<sup>15,20,42-46</sup> Therapy begins with removal of any identifiable offending antigen that affords a 96% cure rate.<sup>21</sup> Antihistamines and corticosteroids have proven efficacious.<sup>21-23</sup> In severe cases electrocoagulation,<sup>47</sup> endoscopic resection of bladder mass,<sup>20,27</sup> partial cystectomy,<sup>7,12,20,30,45</sup> radical cystectomy with reconstruction,<sup>27</sup> or prostatectomy<sup>19,44,47</sup> have been required.

## MATERIALS AND METHODS

Between 1984 and 2005 (inclusive) 10341 bladder specimens (biopsies or resections) were identified in the anatomic pathology archives of the State University of New York Upstate Medical University, Syracuse. Nine hundred forty-seven of these noted cystitis in male patients. These specimens and corresponding medical records were reviewed in accordance with institutional review board guidelines. We looked for the features of acute and/or chronic stage EC in all biopsies 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 observed to avoid potential spurious inclusion of inappropriate cases (some biopsies had limited material). Bladder biopsies with marked and extensive eosinophilic infiltrate were selected. Individual biopsies were regarded as morphologically consistent with EC if the infiltrate exceeded an average of 1 or more eosinophils per HPF. Biopsies with fewer eosinophils but with clinical

| Extended                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                               |                                             |                                        |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|----------------------------------------|
| Biopsy of Acute Phase                                                                                                                                                                                                                                                                                         | Biopsy of Chronic Phase                                                                                                                                                                                       | Therapy                                     | Outcome                                |
| Intense eosinophilic infiltrate extending from the mucosa into the muscular wall, small areas of necrosis and Charcot-Leyden crystals were noted                                                                                                                                                              | NA                                                                                                                                                                                                            | Stopped Coumadin, fulguration               | Cleared in a few days                  |
| I. Recurrent urothelial carcinoma and numerous eosinophils in the lamina propria, few iron-laden macrophages, areas of ulceration and necrosis<br>II–IV. Marked eosinophilic infiltrate of the bladder wall. In addition, a few iron-laden macrophages were noted as well as areas of ulceration and necrosis | V. Plasma cells, mast cells, and a few eosinophils, and moderate fibrosis later—marked fibrosis with rare inflammatory cells<br>VI. Marked fibrosis with rare inflammatory cells (2 y after the first biopsy) | None for EC                                 | No symptoms after                      |
| Urothelial carcinoma in situ, marked eosinophilic infiltrate extending deep in the submucosa and the muscular layer                                                                                                                                                                                           | NA                                                                                                                                                                                                            | Transurethral resection of the bladder neck | Residual penile pain                   |
| I. Eosinophilic infiltrate extending deep in the lamina propria<br>II. Mixed inflammatory infiltrate composed of eosinophils, plasma cells, and a few lymphocytes<br>Numerous eosinophils in the bladder wall                                                                                                 | III. Fibrosis of the bladder wall with numerous plasma cells as well as scattered eosinophils and mast cells—2 y after the second biopsy<br>NA                                                                | None<br>Removal of calculus                 | No symptoms after<br>No symptoms after |
| Edema, fibrosis, foci of necrosis, numerous eosinophils and chronic inflammatory cells                                                                                                                                                                                                                        | NA                                                                                                                                                                                                            | Spasmolytic medication, antibiotics         | No symptoms after                      |
| Multiple foci of necrosis, an intense eosinophilic infiltrate                                                                                                                                                                                                                                                 | NA                                                                                                                                                                                                            | Dissection of urethral strictures           | No symptoms after                      |
| Ulceration with granulation tissue, hemorrhage, and edema, areas with a dense eosinophilic infiltrate and areas with fibrosis                                                                                                                                                                                 | NA                                                                                                                                                                                                            | None                                        | No symptoms after                      |

history of chronic or repeated repetitive episodes of bladder pain were examined for the presence of fibrosis, mast cells, plasma cells, and eosinophils. Clinical features were reviewed in patients with bladder eosinophilia to exclude interstitial cystitis, a distinct clinical entity that may exhibit morphologic overlap with the chronic phase of EC.<sup>48</sup> However, features such as mucosal ulceration covered by fibrin and a mononuclear infiltrate rich in mast cells are characteristic to interstitial cystitis but are not encountered in the chronic phase of EC. The chronic phase of EC presents with an inflammatory infiltrate containing a variable number of eosinophils and there is muscular fibrosis but no necrosis. Also, the acute phase of EC may present with focal muscular necrosis but this is associated with a prominent eosinophilic infiltrate in which mast cells are inconspicuous.

Eight cases of EC were identified. Patient ages, clinical symptoms, morphologic features, associated conditions, endoscopic findings, therapeutic approaches, and outcomes for all 8 were investigated and are presented in the Table.

## RESULTS

Ages ranged from 18 months to 79 years. All patients had at least 1 eosinophil per HPF ( $\times 40$  magnification). This is an equivalent density to the one reported by Yamada and Taguchi.<sup>49</sup> Most patients had one or more associated genitourinary conditions such as prostatic hyperplasia (patients 4 and 7), lithiasis (patients 2 and 5), indwelling Foley catheter (patients 1 and 3), urinary tract infections (patients 1, 6, and 7), irritable bladder symptoms (patients 3 and 4), and urethral strictures (patient 7). Associated surgeries included abdominal perineal colectomy (patient 3, rectal carcinoma), transurethral resection of the prostate (patient 3, hyperplasia), and

bladder neck resection (patient 3, outlet obstruction). Associated malignancies included genitourinary primaries as urothelial carcinoma (patients 2, 3, and 7), rhabdomyosarcoma (patient 6), and malignancies involving other systems including chronic myelogenous leukemia (patient 8) and rectal carcinoma (patient 3). Atopic/allergic conditions such as asthma (patient 7), celiac disease (patient 4), and febrile transfusion reaction (patient 6) were also noted. Patient 3 exhibited a lupus anticoagulant, discovered during the EC episode. All but one patient had repeated episodes of EC. Patient 5 had only one episode of EC related to bladder calculi, resolving without further bladder complaints. Although all 8 patients had biopsy-proven EC, not all EC episodes prompted biopsy. All patients (except patients 2 and 4) had bladder biopsy during the acute phase only. Patient 3 illustrates the clinical presentation, episodic occurrence, and morphology typical of EC (Figure 1). Patients 2 and 4 had several bladder biopsies performed (6 and 3, respectively). The initial biopsies showed numerous eosinophils, edema, hemorrhage, and rare foci of necrosis. These findings were followed in subsequent biopsies by fibrosis of the bladder wall with predominance of plasma cells, mast cells, and only rare eosinophils. Patient 6 showed foci of both acute and chronic phase, simultaneously (Figures 2 and 3). The outcome of most of our patients was favorable; after appropriate management, the symptoms resolved. However, patient 3 experienced continued genitourinary issues, with bladder symptoms for more than 9 years with late development of penile pain.

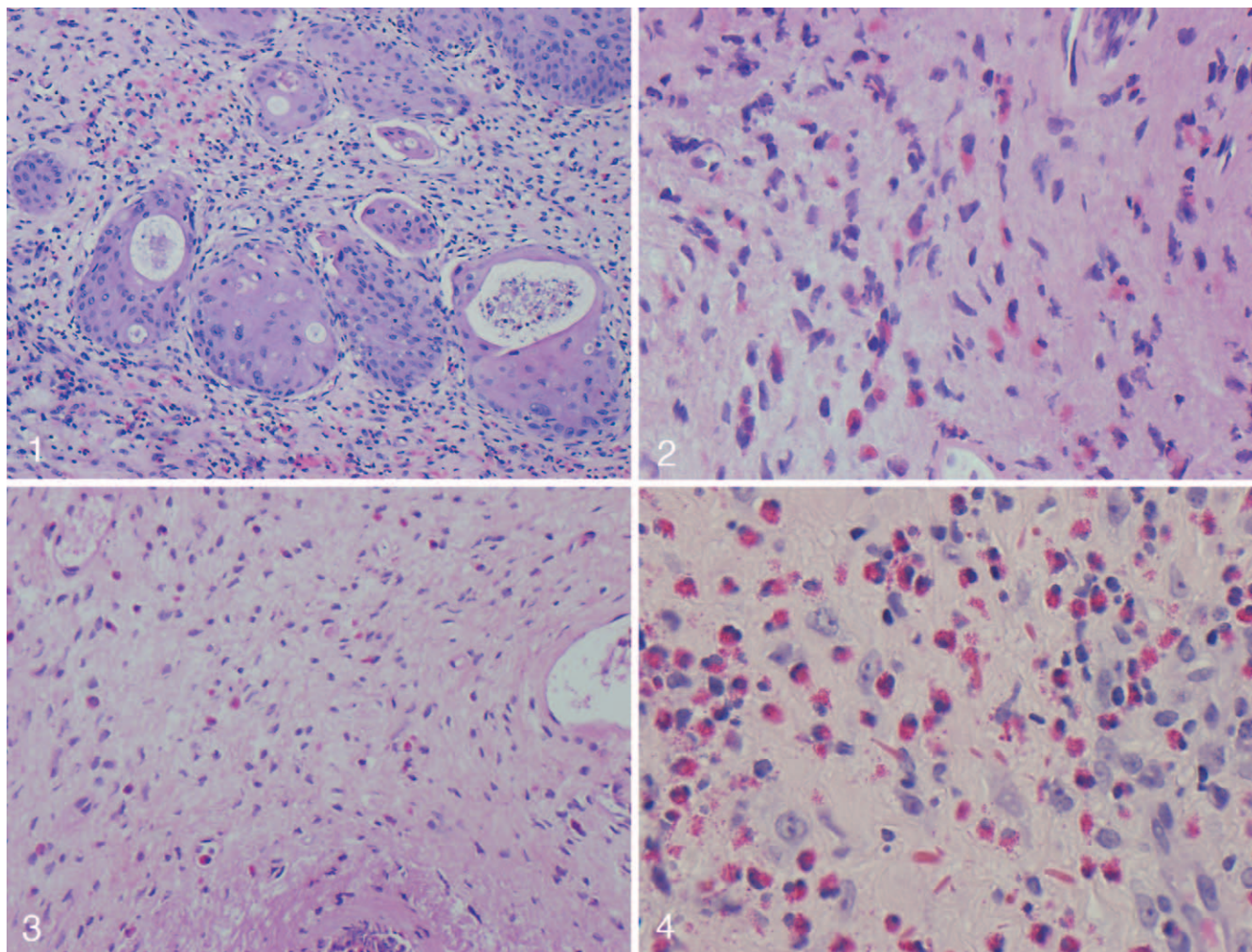


**Figure 1.** Patient 3. A dense leukocytic infiltrate adjacent to a focus of urothelial carcinoma is present in the biopsy. This illustrates eosinophilic cystitis, acute phase, with edema and an infiltrate composed of eosinophils and plasma cells (hematoxylin-eosin, original magnification  $\times 10$ ).

**Figure 2.** Patient 7. An earlier biopsy shows far more prevalent eosinophils (hematoxylin-eosin, original magnification  $\times 40$ ).

**Figure 3.** Patient 7. There is early fibrosis in the chronic phase with a few eosinophils still present (hematoxylin-eosin, original magnification  $\times 20$ ).

**Figure 4.** Patient 1. The bladder wall shows a marked eosinophilic infiltrate with numerous Charcot-Leyden crystals (hematoxylin-eosin, original magnification  $\times 40$ ).

## COMMENT

Eosinophilic cystitis is a rare condition, one that may go unrecognized, especially in the chronic phase and especially in males. Eosinophilic cystitis should, however, be a diagnostic consideration in all patients with frequent and unexplained bladder or other genitourinary complaints. Correlation of all patient bladder biopsy material (current and previous) with clinical history is necessary for arrival at a correct impression and management plan. Eosinophilic cystitis is not a distinct diagnostic entity but rather represents a response to a variety of agents and is encountered in an ever-growing number of conditions. Most reports of EC are based on individual cases or small series although more comprehensive studies have been conducted.<sup>4,22</sup> Hellstrom et al<sup>23</sup> studied EC in 16 male patients. Study of the literature regarding EC in male patients shows a strong association with genitourinary conditions compared with female patients but there are no differences regarding age distribution and clinical outcome. Our study bears out the findings of prior reports and validates

the criteria of Yamada and Taguchi<sup>49</sup> who reported 20 or more eosinophils per five  $\times 20$  fields (comparable eosinophil density). A prominent eosinophilic infiltrate (at least 1 eosinophil per HPF in at least 10 HPFs or Yamada and Taguchi<sup>49</sup> criteria) associated with edema and occasional muscle necrosis are features of the acute phase of EC. Less numerous eosinophils with lymphocytes, plasma cells, and mast cells and muscle fibrosis define the chronic phase of EC. New observations include Charcot-Leyden crystals (Figure 4) and association with celiac disease, lupus anticoagulant, and new viral and bacterial infectious agents. Charcot-Leyden crystals, often encountered in asthma or other eosinophilic disorders, have not previously been noted (by light microscopy) in EC (1 report describes them, ultrastructurally).<sup>33</sup> Association with celiac disease, likewise, has not been previously reported. Celiac disease is related to gluten intolerance. The numerous bouts of EC, viewed on a background of celiac disease (patient 4), suggest a possible underlying immunologic dysfunction at work in both processes. Association of lu-

pus anticoagulant, a condition related to antiphospholipid antibodies, and EC has not been previously reported. Antiphospholipid antibodies may play a role in the generation of EC or may be generated secondary to the tissue damage occurring in EC, although no mechanism linking EC and lupus anticoagulant is known. BK virus infection of the urinary bladder has not been previously reported in association with EC. Hemorrhagic cystitis is the clinical correlate of BK viral bladder infection and is a well-known complication following allogeneic hematopoietic stem cell transplantation.<sup>50</sup> Numerous reports of hemorrhagic cystitis exist, but none has correlated the clinical with the pathologic findings, recognizing the biphasic temporal pattern of EC. *Enterobacter* and *Proteus mirabilis* are 2 microbial agents not previously observed in association with EC. Cultures revealed both organisms in the setting of a bladder mass (patient 6) thought initially to be recurrent rhabdomyosarcoma. Many of the clinical, imaging, and morphologic findings and outcomes in our study are concordant with previous reports. Several patients (patients 1, 6, and 7) had repeated bacterial urinary tract infections. Five (patients 2, 3, 4, 5, and 7) exhibited association of EC with prostatic hyperplasia, bladder stones, prostate or bladder surgery, or medication as detailed in the Table. In the literature most cases of urothelial carcinoma-associated EC have developed after chemotherapy. Only one report notes EC at the time of diagnosis of urothelial carcinoma, prior to chemotherapy.<sup>17</sup> Two of our EC patients presented with urothelial carcinoma, one with recurrent invasive carcinoma and one with carcinoma in situ, the latter patient prior to any intravesical chemotherapy. Patients 2 and 4 illustrate, through serial biopsies, the characteristic temporal pattern of morphologic findings in EC. The initial biopsies revealed marked eosinophilic infiltrates with occasional foci of necrosis and ulceration. Subsequent biopsies showed a predominantly eosinophilic infiltrate but with increasing numbers of lymphocytes and plasma cells. Later biopsies showed many plasma cells and marked fibrosis as well as some mast cells and only scattered to rare eosinophils.

Current thought regarding therapy is summarized in a recent management algorithm,<sup>51</sup> which calls for withdrawal of any identifiable precipitating factor. If none is evident, laboratory studies (urinalysis and culture) and cystoscopy with biopsy are recommended. Nonsteroidal anti-inflammatory agents and antihistamines are favored first-line agents. In refractory cases corticosteroids, cyclosporine, and azathioprine are recommended considerations. Ultimately, if medical management fails, cystectomy may be necessary. Long-term follow-up is recommended for all patients.

Eosinophilic cystitis remains an important, albeit infrequent condition in males evaluated for diverse genitourinary tract symptomatology. Accurate diagnosis is critical because EC therapy is unique and, with identification and withdrawal of precipitating agents, treatment is curative in most individuals. Diagnosis hinges on clinical assessment and histopathology, recalling the temporally biphasic morphologic features. Presence of Charcot-Leyden crystals may offer a clue in acute phase biopsies. Finally, a diagnosis of EC should raise consideration of the possibility of concurrent associated malignancy or other associated conditions.

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