CASE REPORT

Obstructive Uropathy Complicating Eosinophilic Cystitis

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Eosinophilic cystitis is a rare clinicopathologic condition characterized by predominance of eosinophils throughout the bladder wall. The exact disease mechanism is still being debated. However, it is highly associated with atopy and other immunologic conditions. Reported here is a case of eosinophilic cystitis that presented with irritative voiding symptoms with right-sided flank pain, peripheral eosinophilia, and unilateral obstructive uropathy on imaging. Diagnosis was confirmed and documented with cystoscopy and bladder biopsy. Obstructive uropathy was managed with urinary diversion using double J stent. Immunologic signs and symptoms were treated with corticosteroid and antihistamine. Additionally, irritative voiding complaint was managed with antimuscarinic drug. Patient's condition is now on remission with normal eosinophil count and creatinine levels, and normal urinalysis. Resolution of obstructive uropathy and bladder pathology were noted on follow up imaging and cystoscopy, respectively.

Key words: Bladder biopsy, cystoscopy, eosinophilia, eosinophilic cystitis, obstructive uropathy

Introduction

Eosinophilic cystitis is a rare clinicopathologic condition of the urinary bladder that is characterized by predominance of eosinophils in bladder wall.[1] Since its first description by Brown and Palubinskas in the 1960s, a little more than 200 cases were reported in recent literature.[2,3] Many disease mechanisms have been proposed, but the exact cause is still debated.[4] It is thought to be highly associated in patients with atopy and other immunologic conditions. However, other cases are incidentally found in bladder injury secondary to other bladder and prostate disorders. Notably, the disease arises in cases of genitourinary parasitic infections.[5] The clinical and pathologic presentations may vary from mild bladder inflammation to chronic bladder fibrosis, which may result to obstruction and renal failure.[6] Presented here is a case of a Filipino-American female diagnosed with EC based on cystoscopy and bladder wall biopsy.

The Case

A 27-year-old Filipino-American female presented with two months history of urinary frequency, urgency, and dysuria, which was associated with right-sided flank pain and persistent fever lasting for days. CT stonogram showed dilation of right pelvis and proximal ureter with periureteral stranding densities in the middle ureter. (Figure 1) No calcific densities or masses were noted. Urinary bladder was well distended without wall thickening or intraluminal filling defects. Subsequent referral to the Urology service was made. Initial impression was

pyelonephritis secondary to right-sided obstructive uropathy, to consider ureteral stricture. Complete blood count showed eosinophilia with differential count of 22% (NV 0-7%). Serum creatinine was normal. Urinalysis was positive for nitrites, leukocytes, blood, and protein. Urine flow cytometry showed RBC 4/HPF (NV 0-2), WBC 15/HPF (0-3), Bacteria 2153/ HPF (0-50). Urine CS yielded 2 organisms: Escherichia coli and Acinetobacter iwolfii both with counts of 40000 cfu/mL and sensitive to Ertapenem. Past medical history revealed that she had bronchial asthma since childhood, which is controlled by corticosteroid/LAMA inhaler, and perennial allergic rhinitis, which is controlled by desloratadine syrup and sodium chloride nasal spray. She has medication allergies to paracetamol and penicillin-based antibiotics, and food allergies to crustaceans and bivalves. On examination, patient was hemodyamically stable and afebrile. Patient is overweight. No urinary bladder mass or tenderness was noted. The remainder of the physical examination was unremarkable. Ertapenem was given for 24 hours prior to planned procedure. Cystoscopic findings revealed multiple, friable, mixed cystic and solid structures at the bladder floor, with wide-based papillary masses seen underneath the cystic structures, bilateral ureteral orifice were not identified (Figure 2). Transurethral resection of bladder tumor (TURBT) and histopathology result showed benign urothelium with reactive epithelial change consistent with eosinophilic cystitis (Figure 3). Referral with an immunologist was made and laboratory examinations were requested. CBC still showed eosinophilia with differential count of 22% (NV 0-7%). Serum creatinine slightly increased at 1.18 mg/dL. Serum IgE was elevated at 329 IU/mL (NV 0-165 IU/mL). Serum ANA and Kato Katz test were negative. After 5 days, patient proceeded with percutaneous antegrade double J stent insertion in the right ureter.

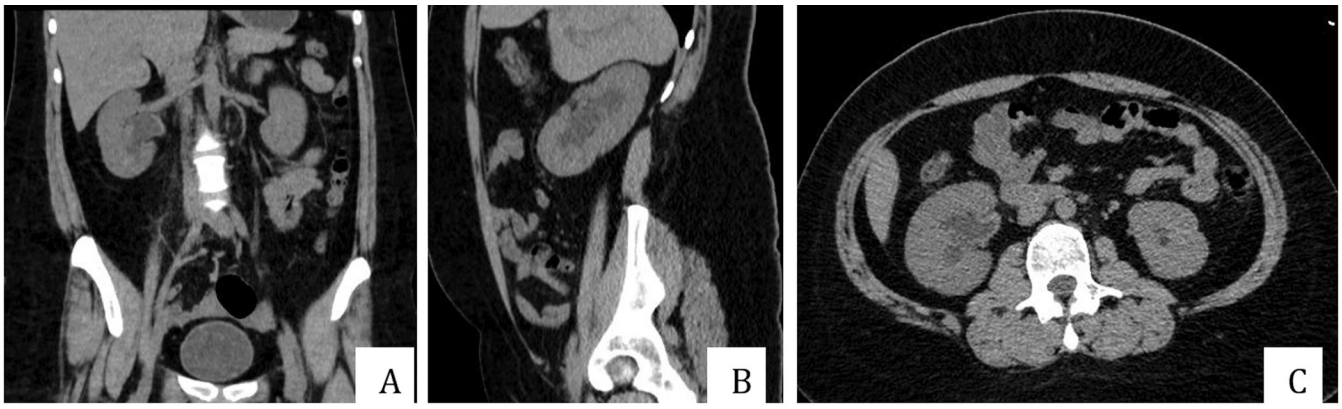

Figure 1. Plain CT scan findings of the patient. A) Coronal view of the right kidney with dilated right renal pelvis and proximal ureter. B) Sagittal view. C) Axial view.

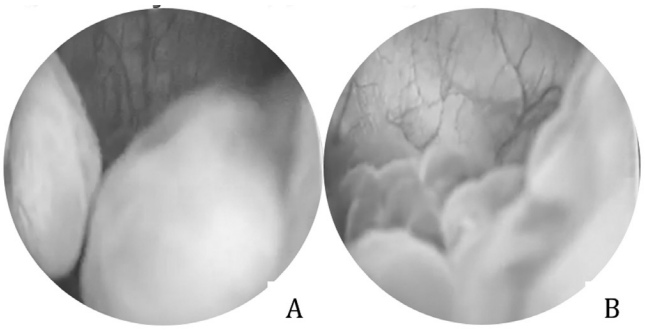

Figure 2. Cystoscopy findings of the patient. Cystoscopy findings showing mixed solid and cystic masses at the bladder neck (A) and floor (B).

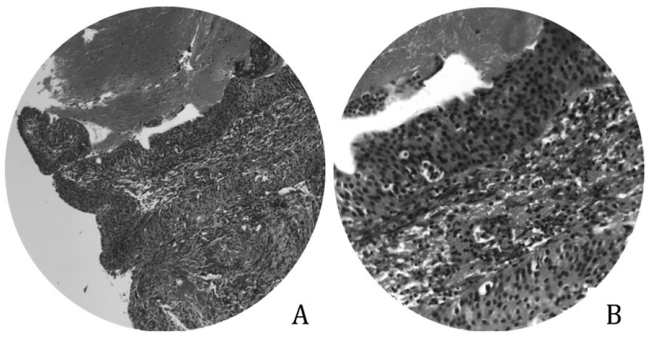

Figure 3. Bladder biopsy from the patient. Eosinophilic infiltrates are seen intersecting the urothelium and lamina propia. A) Hematoxylin-eosin 100x. B) Hematoxylin-eosin 400x.

Postoperative course was unremarkable. The patient was started and discharged with Methylprednisolone 16mg/tablet with tapering dosage, and Cetirizine 10mg/tablet once daily. On follow up one week later, patient was well with no further episodes of flank pain. Repeat CBC noted resolution of eosinophilia and serum IgE was still elevated at 419 IU/ml. The Double J stent was removed after 2 months and noted no complications. Succeeding CBCs have low eosinophil counts, however, serum IgE's were still elevated (281, 359 IU/ml.) The patient was maintained on Mirabegron 50mg/tablet once daily, Methylprednisolone 4mg/tablet once daily, and Cetirizine 5mg/tablet once daily for 3 months.

Discussion

Eosinophilic cystitis (EC) is a rare inflammatory disorder that is characterized by its transmural infiltration of the bladder wall by eosinophils.[1,5] EC has been reported in all age groups with mean age of 41.6 years old.[7] The distribution is equal among male and female in adults. Meanwhile, males are twice affected than females in the pediatric population.[7,8] There is no known genetic predisposition, although, EC has been mostly associated with allergic disorders and atopy. Few cases were incidentally found in bladder injuries secondary to other bladder and prostate disorders.[5] In the present case, the patient has a personal history of bronchial asthma and allergic rhinitis.

The exact pathophysiologic mechanism in developing EC remains unclear. However, the key cytokines that are suggested to be involved are interleukin 3 (IL-3), interleukin 5(IL-5), and granulocyte monocyte colony stimulating factor (GM-CSF). T cells CD4 and CD8 from blood and tissues produce these three cytokines as part of a cell-mediated immune response to offending antigens. These cytokines are responsible for the bone marrow production and peripheral activation of eosinophils in tissues. Eosinophils in turn have complex pro-inflammatory effects including direct cytotoxic effects on tissues, thrombosis, fibrosis, angiogenesis, tissue remodeling, and platelet and endothelial cell activation. Eosinophils themselves produce IL-5 that can trigger a vicious cycle of events leading to the chronicity of the disease.

Patients with EC typically presents with dysuria, gross hematuria, suprapubic pain, and irritative symptoms of frequency/urgency.[6-10] Less common manifestations include the presence of multiple bladder masses, urinary retention resulting to renal insufficiency, hypertension, and edema.[11-13]

EC may affect the urinary bladder diffusely or in a localized form, which can be mistaken with a bladder tumor.[13] Imaging may demonstrate urinary bladder mass, irregular wall thickening and dilation of upper urinary tract system. The dilatation of the upper urinary tract may be secondary to the compression of the ureteral orifices brought upon by fibrosis of the bladder wall.[6] The patient manifested with mild right-sided hydronephroureter on CT stonogram. The combination of clinical signs and symptoms, significant atopic background, eosinophilia and the mentioned findings on imaging should warrant a high index of suspicion for EC.[6] Correct diagnosis and timing in the management is crucial to prevent serious complications of the disease.

EC is a clinicopathologic diagnosis. Clinical findings correlated with information from cystoscopy and transurethral bladder biopsies confirm the diagnosis. Cystoscopy findings comprise a wide array of abnormalities from mucosal erythema to fungating masses mimicking a bladder tumor. With cystoscopy alone, it is difficult to distinguish EC from other benign inflammatory and malignant bladder disorders. Hence, a biopsy is indispensable. Histopathologic findings involve a transmural inflammation of the bladder wall with predominance of eosinophils mainly in the lamina propia.[14] The histopathology report noted benign urothelium with reactive epithelial change consistent with eosinophilic cystitis.

Histology can be classified into acute and chronic phases. The acute phase exhibits tissue eosinophilia, mucosal edema, hyperemia, and muscle necrosis. While in chronic phase, there is lesser degree of tissue eosinophilia, variable chronic inflammation, and bladder wall scarring.[14] The lesions may appear in diffuse form or in localized form with no preferential location. Similarly, the severity and chronicity of the disease is difficult to predict given its variable natural history that can occur in a patient. Most had benign course with resolution of symptoms with conservative management, while others had a chronic or recurrent disease state that resulted into

anatomic changes and renal failure. Therefore, the disease may warrant long term monitoring program comprised of periodic blood and urine examinations, imaging, and cystoscopy.

Management of EC is primarily conservative. Removal of the causative factor or allergens accompanied by medical management often results to resolution of inflammation and symptoms. Non-steroidal anti-inflammatory drugs (NSAIDs) and anti-histamines have been used as primary medications and showed good result on most cases.[4,6-10,15] Corticosteroids were used as second line medications for patients not responding with NSAIDs and antihistamines. These drugs enhance stability of lysosomal membranes within inflammatory cells, which prevent release of antibodies and other inflammatory mediators into tissues. Overall, the effect is reduced inflammation.[6,15]

Non-response after for 4 weeks from the aforementioned treatment would warrant the use of third line medications. These include cyclosporine A, montelukast, and pemirolast potassium.[6,15] Montelukast is leukotriene receptor antagonist, and pemirolast potassium is known to inhibit eosinophil chemotaxis.[6] Cases refractory to medical management may permit a more radical approach. Partial or total cystectomy with urinary diversion was performed in patients with severe hematuria. Urinary diversion with ureteral stenting was performed in the present case.[15]

Conclusion

EC is a rare clinicopathologic disorder of the urinary bladder of still undetermined cause. It remains a diagnostic dilemma for many urologists and doctors due to wide-ranging clinical presentation. Clinical and histopathologic correlations are therefore necessary to establish diagnosis. Conservative approach involves removal of offending agents, followed by administration of NSAIDs, antihistamines, and corticosteroid. Furthermore, it may resort to more radical methods such as cystectomy with urinary diversion in refractory cases. Long term follow-up with periodic laboratory examinations and imaging are necessary.

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