

Case Report

A conservative treatment for eosinophilic cystitis

Franco Alchiede Simonato,¹  Nicola Pavan,²  Mirko Pinelli,² Gabriele Tulone,² Rosa Giaimo,² Anna Martorana³  and Alchiede Simonato² 

¹University of Genoa, Urology Clinic, Genoa, ²Departments of Surgical, Oncological and Stomatological Sciences and ³Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties, University of Palermo, Palermo, Italy

Abbreviations & Acronyms

bmb = bone marrow biopsy

CSS = Churg-Strauss

Ssyndrome

CT = computerized

tomography

EC = eosinophilic syndrome

HES = Hypereosinophilic

syndrome

TUR = transurethral

resection

Correspondence: Nicola Pavan, M.D., FEBU, Urology Clinic, Department of Surgical, Oncological and Stomatological science, University of Palermo, Via del Vespro, 129 90129 Palermo, Italy. Email: nicpavan@gmail.com

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Introduction: Eosinophilic cystitis is a rare condition which causes common symptoms and may mimic other conditions. Eosinophilic cystitis has several causes such as hypereosinophilic syndrome, inflammatory diseases, neoplasia, parasites or fungal infection, IgE-related diseases, Drug Reaction and Eosinophilia and Systemic Symptoms (DRESS) syndrome, or Churg-Strauss syndrome. Therefore, differential diagnosis is difficult.

Case presentation: We report the case of a middle-aged man affected by eosinophilic cystitis with persistent hematuria and other peculiar symptoms that may be brought back to hypereosinophilic crisis.

Conclusion: Conservative approach is preferred, avoiding radical cystectomy rather than corticosteroid, antihistaminic and second line therapy. Hyperbaric therapy is an innovative approach for severe relapsing gross hematuria without specific literature and should be studied for further indications.

Key words: conservative therapy, eosinophilic cystitis, hematuria, hyperbaric therapy, hypereosinophilic syndrome.

Keynote message

We present a rare case of differential diagnosis in a patient with gross hematuria and/or lower urinary tract symptoms: HES manifested as EC should be considered in differential diagnosis.

Case report

Hypereosinophilia (HE) is an uncommon condition that occurs most frequently in middle-aged males. It has been first classified by Hardy and Anderson in 1968¹ and is defined as the presence of >1500 eosinophils/mm³ in peripheral blood in two samples taken at an interval of at least two months and/or the presence of tissue eosinophilia.^{2,3} HE could be associated with many different causes, such as hypereosinophilic syndrome (HES),² inflammatory diseases,^{2,4} neoplasia,² parasites or fungal infection,^{2,4} IgE-related diseases,² DRESS syndrome,² or Churg-Strauss syndrome (CSS).⁵ It could lead to the development of severe systemic or isolated damages² and/or multiple organ damages,³ such as eosinophilic cystitis (EC), but the pathophysiology is unknown.^{3,6} EC is a relatively rare inflammatory condition of the bladder⁷ and its association with HES is far rarer.³ Patients commonly present with urinary frequency, dysuria, hematuria, and supra-pubic pain, which may lead to a wrong diagnosis of a urinary tract infection.^{6,8} It is difficult to distinguish EC from other forms of cystitis.^{6,9}

Case

A 50-year-old patient presented with hematuria and a mass in the posterior wall of the bladder discovered with an ultrasound scan. He had already been hospitalized months earlier for an ischemic stroke treated with fondaparinux and clopidogrel for a month. Following an episode of melena, he underwent blood transfusions and performed a gastroduodenoscopy, with clinical diagnosis of erosive gastritis with a discrete eosinophilic infiltrate. The anamnesis was

negative for allergies, asthma, or respiratory diseases. Physical examination revealed dark macules alongside the interdigital space of his hands. After a cystoscopy, which confirmed the ultrasound finding, he underwent an endoscopic resection of the lesion with a histological report of polypoid cystitis. Blood transfusions and hemostatic transurethral resection (TUR) surgery were performed due to incoercible hematuria and consequent anaemia. In the following, he was readmitted to the Emergency Room (ER) and underwent further blood transfusions and hemostatic TUR with new biopsy sampling. Cystoscopy showed inflammation of the mucosa and an ulcerated pseudopolypoid lesion on the bottom of the bladder (Fig. 1). The histological examination (Fig. 2) revealed a rich

eosinophilic-giant cell lympho-granulocyte infiltrate with granulomatous aspects and some necrotic focus, in the absence of peripheral hypereosinophilia. The patient returned to the hospital for hematuria after about one week and underwent blood transfusions and hemostatic TUR with biopsy sampling again. The histological examination showed intense chronic inflammation with a large amount of eosinophilic granulocytes, in the absence of microorganisms. Uro-computerized tomography (CT) was performed and the results showed a diffuse thickening of bladder walls, with low capacity and small lumen, enlarged regional and para-aortic lymph nodes. Microbiological testing (Quantiferon, *Mycobacterium tuberculosis* in urine, and *Schistosoma* eggs

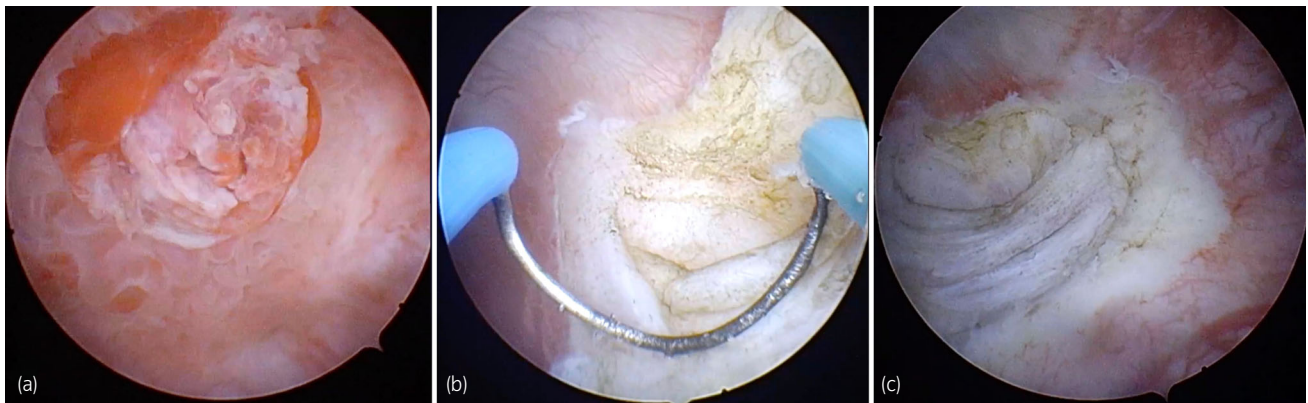


Fig. 1 Cystoscopic images taken during a biopsy for diagnostic assessment: (a) Ulcerated pseudopolypoid lesion on the bottom of the bladder; (b) endoscopic biopsy of the postero-lateral wall of the urinary bladder; (c) resection bed: normal tissue layers are not visible.

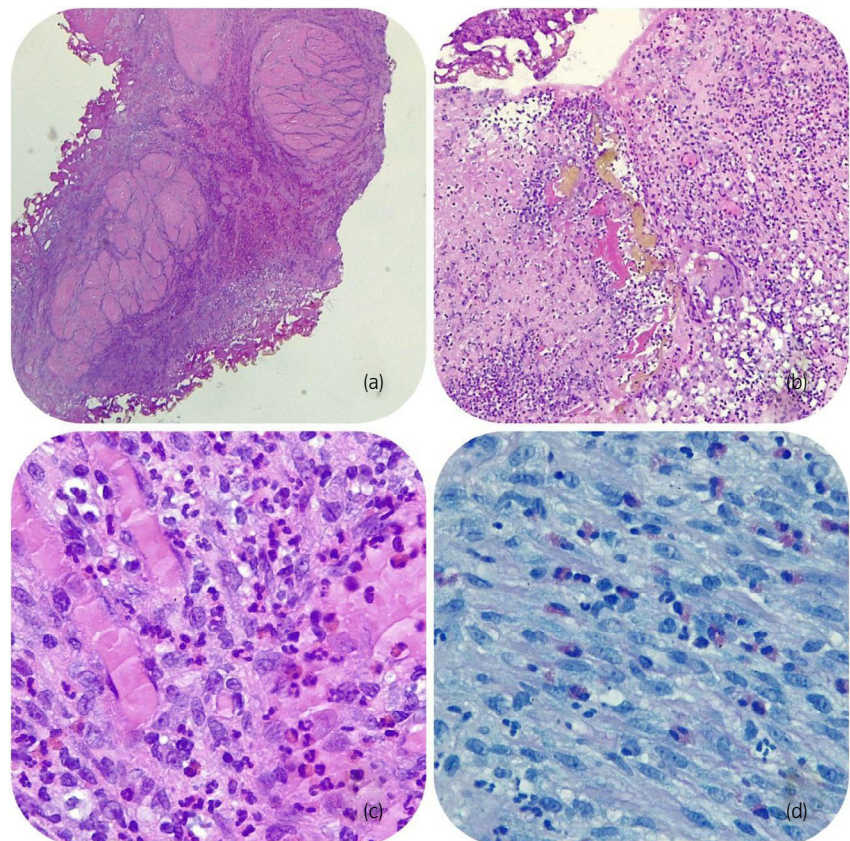


Fig. 2 Biopsy of the posterior wall of the urinary bladder, compatible with the diagnosis of HE. (a) Severe inflammation extended to the muscular layer; (b) occasional multinucleated giant cells and foci of necrosis (hematoxylin-eosin $\times 100$); (c) eosinophilic infiltrate (Hematoxylin-eosin $\times 400$); (d) numerous eosinophils in chorion (Giemsa $\times 400$).

in stool) were performed, all with negative results. As hematologists suggested, the study of coagulation factors and thromboelastogram (TEG) was performed in the suspicion of a hemostasis disease, but with a negative result. Due to gross hematuria, another hemostatic TUR and blood transfusions were performed. The biopsy samples were sent for microbial analysis for the search of parasites, fungi, and bacteria. The result was positive for *Klebsiella pneumoniae* and *Enterococcus faecalis* on histological specimens. The infection was treated with fosfomycin (4 g/thrice a day) and vancomycin (1 g/twice a day). It was decided to avoid radical cystectomy in the young patient. Rheumatological and neurological counseling were required: the rheumatologic etiology was neglected, but antinuclear antibodies (ANA) were found with fine-speckled pattern positivity (1:320); the neurological examination revealed polyneuropathy of upper and lower limbs. After finding total IgE 11 times higher than the cut-off, therapy with Cetirizine (10 mg/die) was set and hyperbaric therapy (2 h/day for 5 days) was performed. Positive urine culture confirmed the infection on the histological finding; therefore, cortisone therapy was postponed. He was discharged with a bladder catheter, cetirizine (10 mg/day), and prednisone (30 mg/day) therapy, in order to keep the disease inactive. The macules and gross hematuria disappeared and polyneuropathy improved, but gross hematuria reappeared with new fondaparinux therapy for orthopedic injury. Triphasic contrast CT highlighted flogosis of the maxillary sinuses and low-capacity urinary bladder with thickening of the posterolateral wall and an effusion nearby the resection area (Fig. 3). Hematochemical analysis showed iron-deficiency anemia and total IgE 3 times higher than the upper limit. An urinary bladder biopsy revealed a rich eosinophilic and lympho-monocytic infiltrate without perivascular fibrinoid necrosis. Rheumatologic counseling excluded vasculitis and hematological counseling suggested to perform a bone marrow biopsy (BMB), which revealed a hypereosinophilic crisis. In addition, research for FIP1L1-PDGFR1 α fusion gene was prescribed. Corticosteroid and antihistaminic therapy was set and hematuria resolved. If symptoms reappear, cystoscopy

will be performed and second line therapy will be considered.

Discussion

In this case, the first manifestation of EC was hematuria, which is a common symptom with multiple differential diagnosis, ranging from bladder cancer to urinary infection. Bladder cancer may mimic EC with polypoid lesions and vice versa,^{4,9} like in this case. Therefore, an endoscopic resection was performed, hematuria continued. Bioptic samples showed eosinophilic infiltration without peripheral eosinophilia. Hyperbaric, antihistamine and prednisone therapy was set and symptoms diminished. Hyperbaric therapy for the reduction of bleeding in EC is not supported by any evidence in literature, but can be performed in radiation cystitis.¹⁰ Parasites and fungal infections were excluded with negative history for recent trips and negative cultures, but biopsy and urine culture revealed a suspected urinary catheter sovra infection by *Klebsiella pneumoniae* and *Enterococcus faecalis*, not relevant for the differential diagnosis. Food or drug allergy reaction history was negative, though IgE in serum were elevated. An incompatible antibody pattern, the rheumatologic and internal medicine counseling, the CT results, and the bioptic examination were not diagnostic for CSS. There are no established guidelines for the management of EC in HES, and there is no known cure for EC³ except for the surgical one.⁷

Table 1 shows five EC case reports with the respective patient characteristics, clinical presentation, treatment, outcome, and follow-up. Four out of six patients were male and two out of six were under 25-years-old. Only one patient was not reported with hematuria and/or eosinophilic bladder infiltration, but he and other four patients had bladder thickening. Four patients underwent prednisone therapy with positive outcome, except for one patient who reported a diminished quality of life.⁸ Nerve sparing subtotal cystectomy and radical cystectomy with orthotopic ileal neobladder with the Vescica Ileale Padovana technique were performed in only two

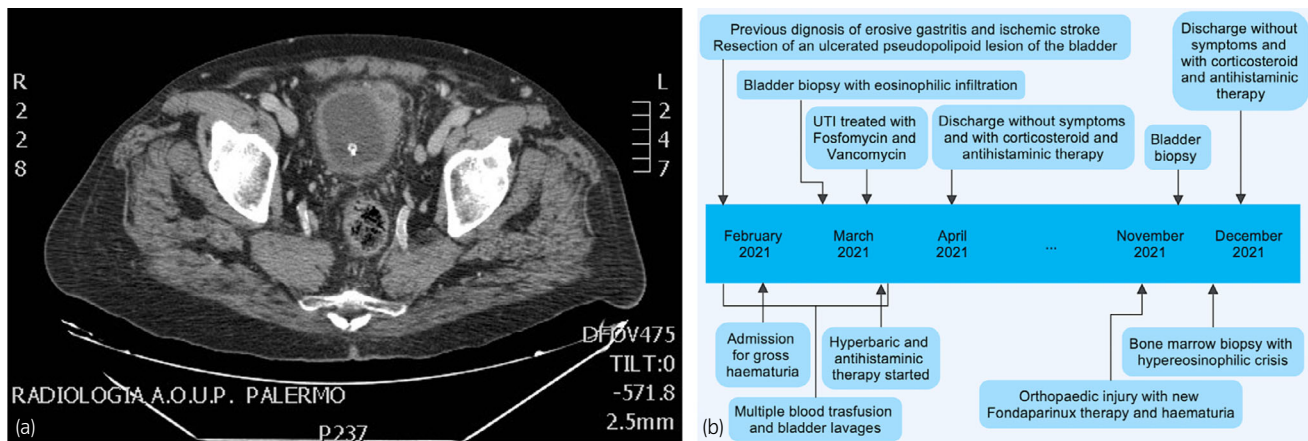


Fig. 3 (a) Uro-CT showing hypervascularization around the bladder, thickening of posterolateral wall, an effusion due to vesical rupture in the anterolateral wall and enlargement of locoregional lymph nodes; (b) chart diagram with time showing the clinical course with symptoms, exams, and therapies.

Table 1 Patient characteristics, clinical presentation, treatment, outcome, and follow-up from other case reports

Reference	Sex	Age	Clinical presentation	Treatment	Dosage	Outcome	Follow-up
Jang2014	M	55	Gross hematuria, leukocytosis, hypereosinophilia, bladder thickening, eosinophilic bladder infiltration	Prednisone	1 mg/kg per day for 6 weeks per os	Bladder infiltration completely resolved. Partial hemological remission	Fluctuant eosinophil count for 6 months
Özdoğan2014	M	8	Terminal hematuria, dysuria, eosinophiluria, hypereosinophilia, diffuse bladder enlargement and thickening, eosinophilic bladder infiltration	Ibuprofen Desloratadine Clarithromycin	10 mg/kg in 3 doses 5 mg/day	Hematuria completely resolved Bladder thickening decreased from 11 mm to 4 mm after 4 weeks of treatment	Still asymptomatic after one year
Chia2016	M	73	Hematuria, dysuria, frequency, bladder thickening, eosinophilic bladder infiltration	Prednisone		Hematuria completely resolved	Still asymptomatic after 4 weeks
Rossanese 2017	M	23	Urinary storage, urinary voiding, bilateral HUN [†] , bladder thickening	Prednisone Nitrofurantoin Levocetirizine Nerve sparing subtotal cystectomy with orthotopic ileal neobladder (VIP [§] technique)	25 mg/day 50 mg/day 5 mg/day	HUN [†] resolved after 6 weeks. Bladder thickness decreased after 6 weeks. No LUTS [‡] after 3 years. Normal renal function after 3 years.	After one month from urinary catheter removal, severe LUTS [‡] recurred.
	M	62	3-year history of recurrent high-risk non-muscle invasive bladder cancer, large erythematous bladder thickening, right HUN [†] , eosinophilic bladder infiltration	Radical cystectomy with orthotopic ileal neobladder (VIP [§] technique)		Normal erectile and ejaculatory function after 3 years. Still asymptomatic after 2 years. No LUTS [‡] after 2 years. No HUN [†] after 2 years.	
Cooke2020	F	78	Dysuria, urinary frequency (20 voidings per day and 20 voidings per night), urinary emergency, urinary incontinence, pelvic pain, hematuria, eosinophilic bladder infiltration	Oral corticosteroids Antihistamines Montelukast Antibiotic suppressive therapy Antispasmodics Benralizumab	30 mg s.c. every 4 weeks	No benefits reported. Self-reported QoL continued to diminish. Urinary frequency reduced (from 20 voidings per night to 4–8)	Continued cystitis with rare eosinophils, after 9 months UDI-6 [¶] increased from 58 to 38, after 9 months Self-reported QoL [¶] and UDI-6 ^{††} increased

†Hydronephrosis. ‡Lower urinary tract symptoms. §Vescica ileale padovana. ¶Quality of life. ††Urogenital distress inventory.

patients with the resolution of all the symptoms.⁷ Antihistamine therapy is reported with resolution of the symptoms^{4,7} especially when associated with prednisone,⁴ but one patient reported a diminished quality of life⁸ and another one relapsed after 1 month from bladder catheter removal.⁷ Treatment with benralizumab reported with a clinical improvement both in outcome and follow-up⁸. Nonsteroidal anti-inflammatory drugs, hydroxyurea, IFN-alpha, mepolizumab, imatinib and other tyrosine-kinase inhibitors, vincristine, 6-mercaptopurine, busulfan, chlorambucil, azathioprine, cyclosporine-A, cytarabine, methotrexate, immunoglobulins, and alemtuzumab were reported for the EC second line treatment.^{2,3,6,8}

In case of gross hematuria and/or lower urinary tract symptoms, HES manifested as EC should be considered in differential diagnosis. BMB and cystoscopy with biopsy should be performed to confirm the suspicion. Major, but not resolving, surgery should be avoided in favor of a conservative therapy. Hyperbaric therapy could be considered to treat EC hematuria and studied for additional indications, such as hematuria.

Ethical statement

An institutional review board approval was not required as this was a single case. The patient provided informed consent.

Conflict of interest

The authors declare no conflicts of interest associated with this manuscript.

Registry and the Registration No. of the study/trial

Not applicable.

Editorial Comment

Editorial Comment to A conservative treatment for eosinophilic cystitis

The authors described a case of difficult-to-diagnose eosinophilic cystitis (EC) that caused recurrent hematuria.¹ EC is an inflammatory disease with eosinophilic infiltration of the bladder wall. Peripheral blood eosinophilia is frequently observed in patients with EC but is not shown in this case. A pooled analysis of 135 patients with EC reported that peripheral eosinophilia (defined as >5% of eosinophilia among leukocytes) occurred in 43% of patients.²

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Author contributions

Franco Alchiede Simonato: Conceptualization; methodology; writing – original draft; writing – review and editing. Nicola Pavan: Conceptualization; formal analysis; writing – original draft. Mirko Pinelli: Conceptualization; supervision. Gabriele Tulone: Investigation; methodology; validation. Rosa Giaimo: Methodology; supervision; validation. Annamaria Martorana: Supervision; visualization; writing – review and editing. Alchiede Simonato: Conceptualization; investigation; supervision; writing – review and editing.

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The definition of hypereosinophilia (HE) includes blood eosinophilia and/or tissue eosinophilic infiltration or increased eosinophils ($\geq 20\%$ of all nucleated cells) in the bone marrow similar to this case; thus, EC is considered part of HE.³ Various HE etiologies have been listed, including infection, drugs such as tranilast, allergy, or parasites. Taking a detailed medical history, such as a foreign voyage or dietary supplement is important to clarify the cause of HE. Additionally, hematologic malignancies, such as chronic eosinophilic leukemia, can also cause HE; therefore, consultation with a hematologist should be considered if pathological findings of the bladder tissue obtained using transurethral resection show eosinophilic infiltration.

There is no consensus on the treatment for EC, and corticosteroids or antihistamines are commonly used, with a relatively