



Hemorrhagic Cystitis with Giant Cells in Rheumatoid Arthritis Treating with Tacrolimus

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Hemorrhagic cystitis is a diffuse inflammation of the mucosa of the bladder, characterized by hematuria and burning upon urination. This might be caused by a variety of reasons, including undergoing chemotherapy (such as cyclophosphamide), radiation therapy, bladder cancer, certain viruses, urinary infections, and thrombocytopenia. There are no previous reports of hemorrhagic cystitis associated with the use of tacrolimus. This is the first case of

hemorrhagic cystitis due to tacrolimus for the treatment of rheumatoid arthritis. We describe a case of hemorrhagic cystitis with giant cells in a patient with rheumatoid arthritis treating with tacrolimus. Hematuria resolved spontaneously with discontinuation of the drug.

Key Words. Hemorrhagic cystitis, Rheumatoid arthritis, Tacrolimus

Introduction

Hemorrhagic cystitis (HC) is a diffuse inflammation of the mucosa of the bladder. It is characterized by gross hematuria and irritating voiding symptoms such as dysuria, with frequency and urgency (1). The reasons behind this may include undergoing chemotherapy (such as cyclophosphamide), using drugs (such as atrovastatin, penicillin G), radiation therapy, bladder cancer, certain viruses, urinary infections, and thrombocytopenia (1,2). In particular, chemotherapy and radiation therapy are the cancer treatment modalities that account for the majority of the causes of this urologic emergency. Tacrolimus is useful for the treatment of rheumatoid arthritis (RA), but has several side effects. We describe the first case of HC, with giant cells, in a 73-year-old female patient with RA, who is being treated with Tacrolimus.

Case Report

A 73-year-old woman was suffering from urinary frequency and gross hematuria for three days. The urine was pink-tinged

with an occasional small clot. She was initially treated, empirically, with sulfamethoxazole/trimethoprim for a presumed urinary tract infection, but showed no change in symptoms. She was referred for further urologic evaluation. The patient denied any prior urologic history, and did not have a history of smoking. She had been treated for RA and interstitial lung disease (ILD, Figure 1A) with corticosteroid and methotrexate (MTX, 10 mg/week), hydroxychloroquine (300 mg/day), and sulfasalazine (2.0 g/day) for four years. She had responded inadequately to above anti-rheumatic drugs and had relative contraindication of MTX and leflunomide due to ILD. Thus, she was treated with corticosteroid and Tacrolimus (3 mg/day) for one year. There was no change in other anti-rheumatic drugs, also any use of cyclophosphamide. Her temperature was 36.7°C, her blood pressure was 116/72 mm Hg, and her pulse rate was 85 per minute. A physical examination revealed multiple tender and swollen joints on both hands, feet, and the right knee. A high ESR of 45 mm/hr. (normal <20/ mm/hr.), C-reactive protein of 13.47 mg/L (normal <5 mg/L), and

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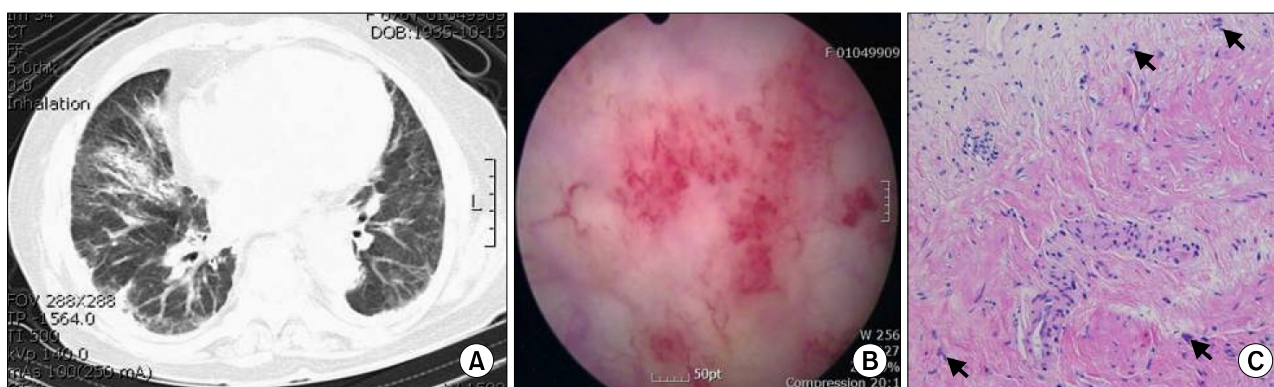


Figure 1. Ground glass appearance of both lower lung fields on high-resolution CT of the lung (A). Cystoscopic examination of bladder showed erythematous mucosa (B) and atypical giant stromal cells in the lamina propria (arrows) showing enlarged, hyperchromatic, multilobulated nuclei were present on histological examination of cystoscopically biopsied bladder mucosal wall (C, H&E, $\times 200$).

rheumatoid factor and anti-CCP antibody were positive. Urinalysis showed many RBC, per high power field, with proteinuria. Urine cultures and cytological evaluations of urine for malignancy were negative three times. Viral cystitis might be one of the most important differential diagnoses. However, immunologic tests for adenovirus, cytomegalovirus, herpes simplex viruses, and BK virus were all negative. Cystoscopic examination showed acutely diffuse, erythematous, inflammatory mucosa, and increased vascularity with fragile vessels (Figure 1B). The histological findings from the cystoscopically biopsied bladder mucosal wall showed the presence of atypical giant stromal cells in the lamina propria (arrows). These showed enlarged, hyperchromatic, multilobulated nuclei (Figure 1C, H&E, $\times 200$). There was no ulceration, with very few mast cells, arguing against a diagnosis of interstitial cystitis. The patient discontinued using Tacrolimus, but continued with the other medication for the treatment of RA. She was treated conservatively, keeping a Foley catheter in the bladder. Her hematuria resolved within two weeks of discontinuation of Tacrolimus. Results from urinalysis at a six-month follow-up visit were negative. She has since been followed for 12 months, without the recurrence of hematuria with infliximab therapy, at the out-patient department. Her articular symptoms have improved.

Discussion

The bladder is vulnerable to the adverse effects of many drugs because of its intimate exposure to toxins and drug metabolites in the urine (3). One of the very rare adverse reactions to several drugs is HC. This results from damage to the bladder transitional epithelium and blood vessels by toxins, drugs, viruses, radiation, or disease (1,2). This is a well-described complication of cancer treatment for patients

undergoing hematopoietic stem cell transplantation, bone marrow transplantation, or rheumatic diseases. The most common cause of drug-induced HC is acrolein, a metabolite of the chemotherapeutic agents, cyclophosphamide and isophosphamide (4). The bladder toxicity of cyclophosphamide is dose related and thought to be secondary to the reservoir's prolonged contact time with acrolein. Several case reports have implicated penicillin as a cause of HC. Penicillin-induced HC is thought to be caused by an immune-mediated hypersensitivity, because urine frequently reveals eosinophilia (5). An isolated case of HC has also been reported with danazol use in a patient with hereditary angioedema, with unclear etiology (6), and atorvastatin (7).

Tacrolimus is a drug that suppresses the immune system and is used to prevent the rejection of transplanted organs. It accomplishes its immune-suppressing effects by inhibiting an enzyme (calcineurin) that is crucial for the multiplication of T-cells, which are vital to the immune process (8). It also has been used for the treatment of myasthenia gravis, lupus nephritis, and ulcerative colitis. In addition, it was approved for RA patients who showed an inappropriate response to conventional treatments. The most commonly reported adverse drug reactions (occurring in $>10\%$ of patients) are tremors, renal impairment, hyperglycemic conditions, diabetes mellitus, hyperkalemia, infections, hypertension, and insomnia. Renal and urinary adverse reactions include renal impairment, renal tubular necrosis, toxic nephropathy, and bladder and urethral symptoms. Although nephropathy and HC have been identified as possible (albeit very rare) adverse reaction to Tacrolimus (9), there has been no reported case of HC with giant cells, until now.

RA is a systemic inflammatory disease, characterized by extra-articular organ involvement. Although the involvement of

renal and urinary systems in RA is rare, low-grade membranous nephropathy, glomerulitis, vasculitis, and nephrotic syndrome due to secondary reactive amyloidosis, have all been described. Furthermore, three cases of massive hematuria due to bladder amyloidosis, in patients with RA, have been reported (10). However, in this case, cystoscopic biopsy and histologic examination showed atypical stromal cells with enlarged hyperchromatic multilobulated nuclei in the lamina propria. Therefore, we excluded bladder amyloidosis.

HC has a heterogeneous clinical course that ranges from asymptomatic microscopic hematuria to massive bleeding necessitating blood transfusions, with or without obstructive renal failure (1). Laboratory values of the coagulation profiles and platelet count were generally normal, and urine culture and immunologic tests for viral infections were negative (1). Cystoscopic findings reveal acutely diffuse inflammation as increased vascularity with fragile "corkscrew" vessels (1). HC grading system for severity evaluation has been proposed by Droller et al. (11). for hemorrhagic cystitis. Grade 0: no symptoms of bladder irritability or hemorrhage, Grade 1: microscopic hematuria; Grade 2: macroscopic hematuria, Grade 3: macroscopic hematuria with small clots, Grade 4: massive macroscopic hematuria requiring instrumentation for clot evacuation and/or causing urinary obstruction. In this case, the patient was classified as Grade 3 due to gross hematuria with small blood clots, proteinuria, and urinary frequency without abnormalities of coagulation tests and urinary cultures. Although HC has been reported in worldwide marketing experience with Tacrolimus, the causal relationship to drug exposure was not known. In addition, HC with giant cells has not been reported in association with the use of this drug, until now. It should be differentiated from radiation or chemotherapy-related atypia, sarcomatoid urothelial carcinoma, and primary bladder sarcoma (2).

Giant cell cystitis presented atypical mononucleated, or multinucleated, stromal cells. These findings are common in the lamina propria of the bladder. In addition, these cells are common in routine biopsies without other evidence of cystitis (12). The nuclei are often irregular in size and shape and typically hyperchromatic. Mitotic figures are absent or rare. Similar cells may be seen in the lamina propria after radiation therapy and chemotherapy. One case of hemorrhagic cystitis revealed multinucleated and mononuclear giant cells in a patient with herpes simplex virus type 2 in the bladder mucosa (2).

The management of HC is usually initiated by discontinuing, or reducing, the use of the drug responsible. Intensive intravenous hydration and forced diuresis can be used to dilute uri-

nary toxic metabolites, minimizing their toxicity. Intravesical instillation of formalin, alum, and prostaglandin E1 and F2, has been used to treat chemotherapy-induced HC (13). The systemic administration of conjugated estrogen, hyperbaric oxygen treatment, and the use of local yttrium aluminum garnet laser therapy, has been reported to be effective (1). In cases of severe hematuria with clot formation and continuous bladder irrigation, using a Foley catheter in the bladder (until residual small clots are removed) is recommended to avoid urinary retention. Cystoscopic evacuation may be required for major clots that cannot be removed by irrigation (1). In cases of massive and life-threatening bleeding, surgical intervention such as cystectomy may be indicated. However, in cases of no obstructing blood clots, and if the patient is voiding well, hydration with careful observation may be the only treatment required. In this case, although the patient presented gross hematuria with blood clots, no obstructing blood clots were observed. Our patient's condition was improved after stopping Tacrolimus, maintaining the conservative treatment with hydration and keeping the Foley catheter in the bladder to avoid urinary retention by blood clot.

Summary

Although there is lack of experimental and epidemiological evidence, it is possible that HC with giant cells can occur in RA during treatment with Tacrolimus. Thus, we propose the recognition of this casual relationship and early diagnosis, and suggest that prompt medical treatment is mandatory to avoid unnecessary investigations and improve the outcome.

References

1. Russo P. Urologic emergencies in the cancer patient. *Semin Oncol* 2000;27:284-98.
2. Nguyen ML, Borochovit D, Thomas G, McClure T, Ruben FL. Hemorrhagic cystitis with herpes simplex virus type 2 in the bladder mucosa. *Clin Infect Dis* 1992;14:767-8.
3. Drake MJ, Nixon PM, Crew JP. Drug-induced bladder and urinary disorders. Incidence, prevention and management. *Drug Saf* 1998;19:45-55.
4. Levine LA, Richie JP. Urological complications of cyclophosphamide. *J Urol* 1989;141:1063-9.
5. Brügger-Andersen T, Reiersen R. A 34-year-old man with hemorrhagic cystitis. *Tidsskr Nor Laegeforen* 2004;124:3075-7.
6. Andriole GL, Brickman C, Lack EE, Sesterhenn IA, Javadpour N, Linehan WM, et al. Danazol-induced cystitis: an undescribed source of hematuria in patients with hereditary angioneurotic edema. *J Urol* 1986;135:44-6.
7. Martinez-Suarez HJ, Wang R, Faerber GJ. Atorvastatin-induced hemorrhagic cystitis: a case report. *Urology*

- 2009;73:681.
8. Sakuma S, Kato Y, Nishigaki F, Sasakawa T, Magari K, Miyata S, et al. FK506 potently inhibits T cell activation induced TNF-alpha and IL-1beta production in vitro by human peripheral blood mononuclear cells. *Br J Pharmacol* 2000;130:1655-63.
 9. Takeuchi T, Kawai S, Yamamoto K, Harigai M, Ishida K, Miyasaka N. Post-marketing surveillance of the safety and effectiveness of tacrolimus in 3,267 Japanese patients with rheumatoid arthritis. *Mod Rheumatol* 2014;24:8-16.
 10. Nakamura T, Yamamura Y, Tomoda K, Tsukano M, Baba S. Massive hematuria due to bladder amyloidosis in patients with rheumatoid arthritis: three case reports. *Clin Exp Rheumatol* 2003;21:673-4.
 11. Droller MJ, Saral R, Santos G. Prevention of cyclophosphamide-induced hemorrhagic cystitis. *Urology* 1982;20:256-8.
 12. Grignon DJ, Sakr W. Inflammatory and other conditions that can mimic carcinoma in the urinary bladder. *Pathol Annu* 1995;30:95-122.
 13. Kopterides P, Theodorakopoulou M, Mentzelopoulos S, Armaganidis A. Cyclophosphamide-induced hemorrhagic cystitis successfully treated with conjugated estrogens. *Am J Hematol* 2005;80:166-7.