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Recurrent and Extensive Idiopathic Granulomatous Ureteritis: A Localized Hyperimmune Disease with Genetic Predisposition

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Abstract

Idiopathic granulomatous ureteritis (IGU) is a rare autoimmune disorder. Multiple case reports led to defining its clinicopathological inclusion criteria in 1997. Surgical resection and primary reanastomosis, of such pseudotumor, were considered its definitive management and a 4-months corticosteroid-therapy was used once for persistent ureteric lesion despite of 3-months stenting. Long-term follow-up of such disease is limited and management of its extensive and recurrent disease is lacking. In our case report, a 47-year-man had history of a biopsy-proven IGU 4 years ago that was treated with resection and ureteral reimplantation in a cystoplastic (augmented) bladder. Moreover, he had received Corticosteroids and Azathioprine for a total of 2 years to avoid recurrence. Two years later, he presented with recurrent abdominal pains, urinary tract infections and ultimately; bladder neck disease. Cystoscopic examination revealed extensive bladder masses and severe left ureteric stricture. Biopsy of the bladder lesions confirmed the idiopathic granulomatous disease. He improved, with immunosuppressive therapy that included 3 months of Corticosteroids and Mycophenolate mofetil followed by maintenance therapy with Mycophenolate mofetil. Previous animal studies have shown local hyperimmune response with malformation of the transitional epithelium in a genetically predisposed mice indicating genetic predisposition with immune-mediated expression. Hence, in our patient, we proposed long-term immunosuppressive therapy and follow-up. In conclusion; our case report confirms the autoimmune etiology of such disorder and provides new line of management of its extensive and recurrent variant.

Keywords

Ureteritis, Granulomatous, Mycophenolate, Genetic

1. Introduction

Focal ureteral disease can be caused by cancer, instrumentation, irradiation, calculi, and inflammation (infection, and autoimmune ones) [1]. Infection may follow local spread of 1) bacterial focus viz. appendicitis, diverticulitis, actinomycosis, pelvic inflammatory disorders, endometriosis, and inflammatory bowel disease; 2) tuberculosis; and 3) schistosomiasis. On the other hands; autoimmune causes include; 1) BCG bladder irrigation for papillary carcinoma of urinary bladder; 2) IgG4-related retroperitoneal fibrosis; and 3) idiopathic granulomatous ureteritis. The latter is extremely rare yet with few well-defined case reports since 1963 [2]. In 1997; its clinicopathological inclusion criteria have been defined and included; 1) a discreet segment of involved ureter; 2) "creeping fat" of the ureter; 3) transmural chronic fibrosing inflammation; 4) mucosal ulceration; 5) marked underlying lympho-plasmacytic infiltrate with fibrosis and vascularization; 6) prominent lymphoid follicles with germinal centers presented in all levels of the ureteral wall and extending into peri-ureteral fat and 7) noncaseating granulomas [3]. By 2017; surgical resection and primary reanastomosis, of such pseudotumor, were considered its definitive management [4] [5]. Despite its autoimmune etiology, immunosuppressive agents were rarely used except for an isolated case of persistent stenosis despite 3-months of stenting which improved subsequent to 4-months oral corticosteroid therapy [6]. Long-term follow-up of such disease is limited and the experience with management of extensive disease recurrence is lacking. In our case report we present a patient with the latter phenomenon who improved with immunosuppressive therapy confirming the autoimmune etiology of such disorder and the need for long-term treatment.

2. The Case

Four years ago; a 47-year-old man presented with recurrent urinary tract infections and lower abdominal pain of 1 year duration. At that time; his investigations revealed hydronephrotic left kidney. CT with contrast showed a 10 cm ureteric stricture at the left vesicoureteric junction. Cystoscopy did not show bladder abnormality and catheterization of ureters had failed. Hence, he had resection of the stenosed left ureteric segment followed by its re-implantation into an augmented bladder (cytoplasty). Histopathological examination of the resected ureter showed non-caseating granulomatous inflammation. TB Elispot test and TB cultures were negative. Bilharziasis and autoimmune screen (ANA, anti-dsDNA, ANCA, anti-GBM) were negative. Subsequent MAG III showed equal kidney function and lack of obstruction in the left ureter. Moreover, he

was treated with Prednisone 60 mg/day for 4 months followed by daily Prednisone 5 mg and Azathioprine 100 mg for 2 years. Two years later; he presented with lower abdominal pain and difficulty in passing urine. He was afebrile, normotensive and with body weight 71 kg. He did not have skin disease or lymphadenopathy. Systemic examination did not show abnormality. Laboratory tests showed normal peripheral leucocytic and platelets counts. Hemoglobin was 110 g/L with normal MCV. Serum urea and creatinine were elevated at 12 mmol/L and 124 umol/L, respectively. Serum sugar, electrolytes and liver functions were normal except for albumin at 30 g/L. Serum cholesterol and TSH were normal. Urine routine and microscopy was normal except for pyuria. Serum complements (C3 & C4), protein electrophoresis as well as IgG4 and IgA levels were normal. ANA, anti-ds DNA, ANCA, anti-GBM-antibodies, RA, hepatitis B surface antigen and anti-HCV antibodies were negative. Stool testing for ova, parasites and occult blood was normal. Upper and lower GI endoscopy were normal. Chest x-ray and ECG were normal. Abdominal and pelvic ultrasound was normal except for 9 cm right kidney and 10 cm left with moderate hydronephrosis and reduced cortical thickness. Urine culture had shown E. coli which was sensitive to Meropenem and had received it. Bone mineral density showed severe osteoporosis with T: −2.9. He had normal vitamin D level and calcium. Hence, he was treated with Prolia every 6 months. MRI study confirmed the smaller sized-kidneys with multiple cortical scars and has shown moderate left hydronephrosis and hydroureter up to its distal end with a 2 cm stricture at vesicoureteric junction (**Figure 1**). Moreover, it did not show para-aortic lymphadenopathy, extra-renal and ureteric masses. Uroflowmetry was done since the patient had severe voiding difficulty. The latter showed revealed a maximum flow at 7 ml/second after voiding of 260 ml of urine. Cystourethroscopy revealed masses in the urinary bladder leading to stenosis of the left ureter and urethra (**Figure 2**). Histopathological examination showed denuded urothelium that

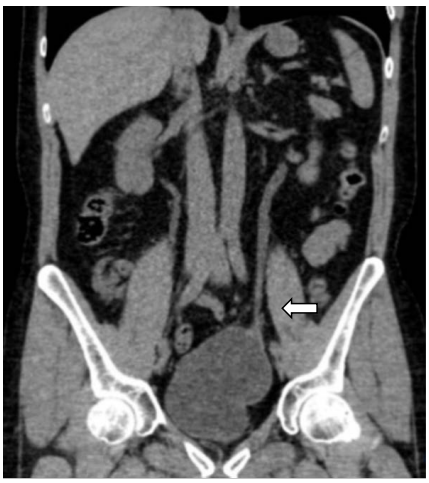

Figure 1. MRI scan showing 10 mm narrowing of the distal ureteric segment (arrow) proximal to a reimplanted, previously-resected, ureteric end into a cystoplastic part of urinary bladder.

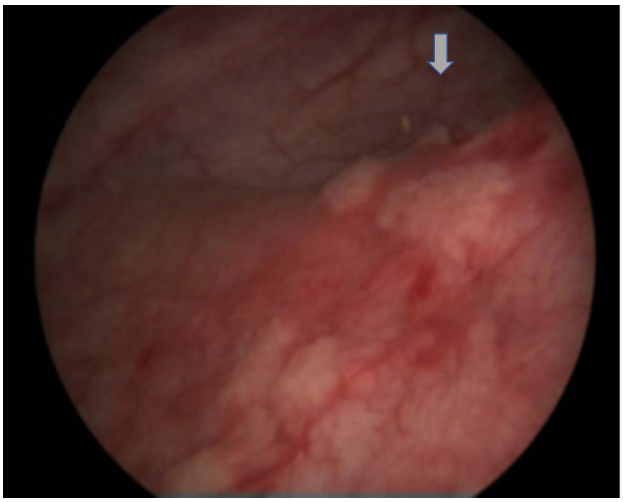

Figure 2. Cystoscopic picture showing multiple well defined, grayish yellow nodules around the stenosed orifice of the re-implanted LT ureter (arrow). Note hyperemia of the surrounding mucosa.

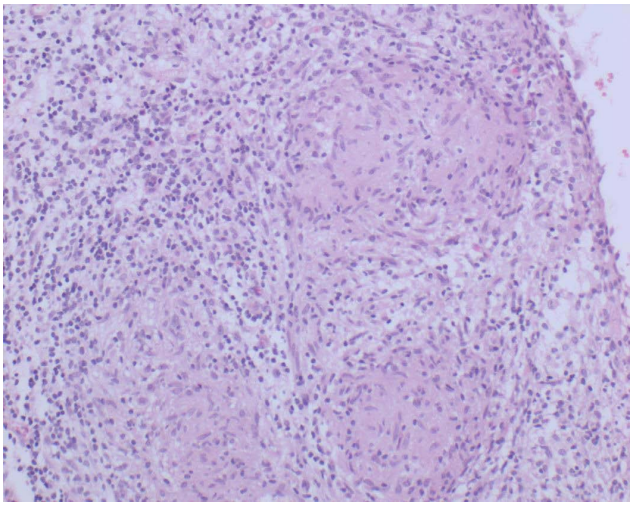

Figure 3. Non-necrotizing granuloma surrounded by dense lymphoid infiltration. The urothelium is denuded (H&E stain, 10× magnification).

lacked atypia. The lamina propria contained multiple non-caseating/necrotizing granulomata with chronic inflammatory cells (**Figure 3**). Deeper tissues and muscles were normal. Stains for IgG-4 were negative. He was treated with Prednisone 60 mg daily that was tapered down after the first month and discontinued by the third month. Moreover, at start, he had received Mycophenolate mofetil 1 g twice daily that was decreased to 500 mg twice daily 1 year later. At present, he finished 2 years of follow up. He is asymptomatic and without urinary tract infections. Serum creatinine remained stable and his serum albumin and hemoglobin returned to normal. Follow up ultrasonography did not show recurrence of hydronephrosis and MAG III studies did not show obstruction. Since he had recurrent and extensive disease; the proposed future plan is to continue such dose of MMF indefinitely.

3. Discussion

Our patient manifested severe stenotic lesions in his urinary tracts which were associated with recurrent urinary tract infections. Biopsy of his initial and subsequent lesions showed non-caseating granulomatous inflammation without eosinophilia and IgG4 disease confirming diagnosis of IGU. The initial surgery corrected his obstructive manifestations and had received Prednisone 1 mg/kg for 4 months and even Azathioprine for 2 years [6]. Unfortunately, 2 years later, his inflammatory disease had recurred and even had progressed to severe ureteral stenosis with further involvement of the urinary bladder with masses and bladder neck obstruction. Restarting treatment with Prednisone 1 mg/kg/day for 3 months with MMF resulted in significant regression of his disease that persisted for >6 months. Such phenomenon of disease development, recurrence and progression indicates local hyperimmune response with malformation of the transitional epithelium in a genetically predisposed patient [7]. Our hypothesis of genetic predisposition is based on analysis of molecular pathology of ureteritis causing hydronephrosis in laboratory rodents [8]. Their stenotic lesions showed extensive infiltration with B-cell lymphocytes and comprehensive gene profiling revealed elevated expression of genes associated with hyperimmune responses through activation of B cells. Furthermore, their diseased ureters showed dramatically higher gene expression of *chitinase 3-like 3*, known as *Ym1*, which was associated with formation of adenomas in the transitional epithelium and of eosinophilic crystals in inflammatory conditions. The Ym1 protein was mainly localized to the cytoplasm of the transitional epithelium, infiltrated cells, and eosinophilic crystals in diseased ureters. In our patient, we preferred MMF as the maintenance immunosuppressive drug for its safe and effective profile as well as its potent antiproliferative action via suppression of both B and T cells via stimulation of CD3/CD28 that inhibits T cell IL-17, IFN-γ and TNF-α production [9]. In conclusion; in our patients; relapse of autoimmune granulomatous inflammation of the urinary tract is in accordance with genetic predisposition of his disease and the need for long-term immunosuppressive therapy.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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