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Management of ureteral IgG4-Related Disease: The great masquerader

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A B S T R A C T

IgG4-related disease (IgG4-RD) is a systemic fibro-inflammatory condition that can mimic malignancies, including ureteric urothelial carcinoma (UCC). This case report describes a 65-year-old female presenting with obstructive uropathy due to IgG4-related ureteritis. Initial imaging suggested UCC, however ureteric biopsy was negative. Elevated serum IgG4 levels (3.77 g/L) supported the diagnosis of IgG4-related ureteritis. Treatment with methotrexate, prednisolone, and rituximab led to significant improvement, with subsequent imaging showing resolution of obstructive uropathy. This case highlights the importance of considering IgG4-RD in the differential diagnosis of ureteric malignancies to prevent unnecessary invasive procedures and optimize patient outcomes through appropriate immunosuppressive therapy.

1. Introduction

IgG4-related disease (IgG4-RD) is a systemic fibro-inflammatory condition characterized by the presence of tumefactive lesions, a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, and elevated serum IgG4 levels.[1] It can affect various organs, including the pancreas, salivary glands, kidneys, and ureters.[2,3] Ureteritis secondary to IgG4-RD is a rare manifestation that can present with features mimicking ureteric urothelial carcinoma (UCC), posing significant diagnostic challenges.[4] Accurate diagnosis is critical to avoid unnecessary invasive procedures and to preserve renal function. Herein, we present a case of IgG4-related ureteritis and secondary obstructive uropathy successfully managed with medical therapy.

1.1. Case presentation

A 65-year-old female presented with a septic obstructed left kidney due to a thickened pelvi-ureteric junction (PUJ). The patient's medical history was notable for breast cancer, rheumatoid arthritis, depression, and hypothyroidism. Her hormone sensitive invasive lobular breast carcinoma was diagnosed in 2014 and treated with neoadjuvant chemotherapy, wide local excision, radiotherapy, and ongoing letrozole for hormonal blockade. Her rheumatoid arthritis was diagnosed in 2004 and was initially treated with 15 mg methotrexate, which achieved remission and was ceased at the time of her breast cancer diagnosis. However, flares of rheumatoid arthritis recurred over the preceding 18 months, particularly affecting the right metacarpophalangeal joints, pelvis and both feet.

At the time of her presentation, CT IVP showed an enhancing soft tissue mass within the renal pelvis extending into the PUJ and proximal ureter, resulting in moderate left-sided hydronephrosis and altered perfusion of the kidney (Fig. 1). Aside from mildly prominent subcentimetre retroperitoneal and axillary lymph nodes, there was no other abnormality seen in the chest, abdomen and pelvis. Initial laboratory findings included an ESR of 20 mm/hr, CRP of 20 mg/L, GFR of >90 ml/min/1.73 m^2 and creatinine at 54 μmol/L. The patient underwent rigid cystoscopy, left flexible ureteropyeloscopy, bladder and left renal pelvis biopsy, and JJ stent insertion. The cystoscopy revealed two bladder tumors at the right bladder neck, which were biopsied. On direct visualisation of the proximal ureter, narrowing at the PUJ was noted with thickened and abnormal urothelium, but there was no obvious papillary tumour typical for UCC. Histopathology revealed a low-grade transitional cell carcinoma (LG pTa) in the bladder and reactive urothelium in the left PUJ biopsy with no malignancy. Atypical urothelial cells were noted in the left ureteric washings, but no malignant cells were seen.

A follow-up FDG PET scan indicated low-grade activity in small left para-aortic lymph nodes and multiple FDG-avid right axillary and subpectoral lymph nodes. Serum IgG levels measured showed elevated IgG1 (12.6 g/L) and IgG4 (3.77 g/L), with a total IgG of 22.0 g/L (Fig. 2). Serum ACE and ANCA were negative. The patient was subsequently reviewed by rheumatology and treatment included methotrexate 20 mg, 5 mg folate, and prednisolone 50 mg daily, tapering gradually. Two months later, CT IVP demonstrated treatment response with a decrease

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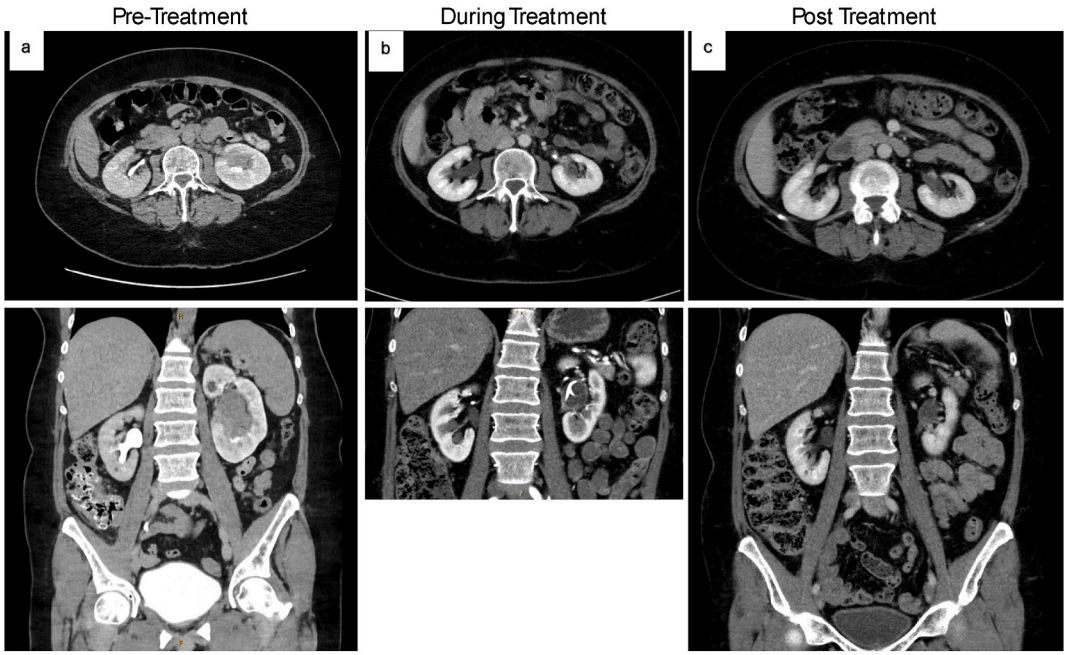

Fig. 1. CT-AP with delayed phase demonstrating (a) significant left hydronephrosis, delayed nephrogram, and renal pelvis ureteric thickening extending to the PUJ pre-treatment, (b) moderate resolution of renal pelvis thickening with stent in situ during treatment, and (c) complete resolution of renal pelvis/PUJ thickening post-treatment. Top row = axial views, bottom row = coronal views.

H	Immunoglobulin G1 (IgG1)	12.60(g/L)	4.05-10.11
	Immunoglobulin G2 (IgG2)	5.86(g/L)	1.69-7.86
	Immunoglobulin G3 (IgG3)	0.61(g/L)	0.110-0.850
H	Immunoglobulin G4 (IgG4)	3.77(g/L)	0.030-2.010
H	Immunoglobulin G (Total IgG)	22.00(g/L)	5.76-15.36
	SE-IGG SUBCLASSES	An elevated IgG4 may be seen in IgG4 related sclerosing disease.	

Fig. 2. Serum IgG titres demonstrating relative elevation of IgG1, IgG4, and total IgG.

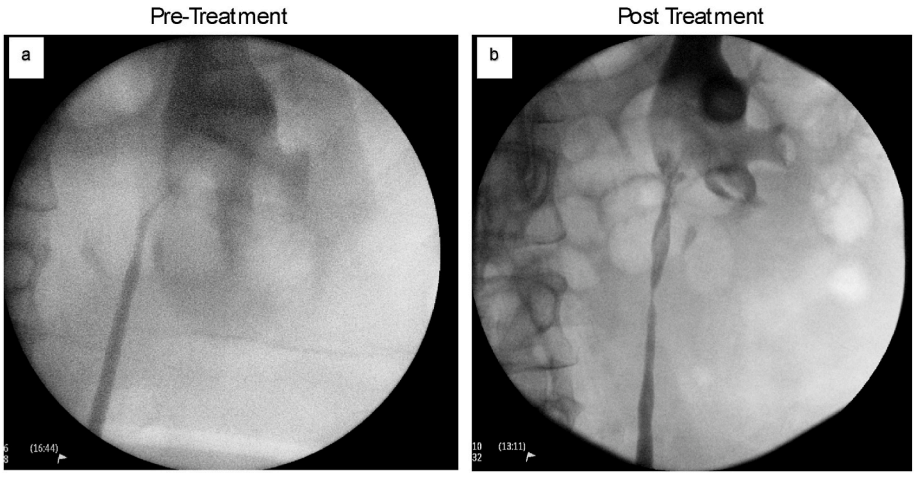

Fig. 3. Retrograde pyelography performed demonstrating (a) pre-treatment filling defect in inferior aspect of left renal pelvis with concentric filling defect of proximal ureter and moderate hydrouretonephrosis; and (b) post-treatment resolution of contrast filling defect previously seen in proximal ureter and renal pelvis.

in mural wall thickening of the left renal pelvis and ureter with resolution of hydroureteronephrosis, and no interval enlargement of retroperitoneal or pelvic sidewall lymph nodes (Fig. 1). Subsequent repeat retrograde pyelography and stent removal revealed persistent but improved narrowing at the PUJ (Fig. 3). Ureteric stent was removed at this time. At her subsequent rheumatological review, ESR decreased from 94 to 35 mm/hr, and CRP was 1 mg/L. The patient commenced rituximab 1g at weeks 0 and 2 as a steroid-sparing agent and treatment for presumed IgG4-RD.

At four months following treatment, follow-up CT IVP and MAG3 with Lasix demonstrated significant reduction in the previously seen mural thickening in the left renal pelvis and ureter, with normal drainage of the left kidney (Figs. 1 and 4), indicating resolution of her IgG4 ureteritis and associated obstructive uropathy.

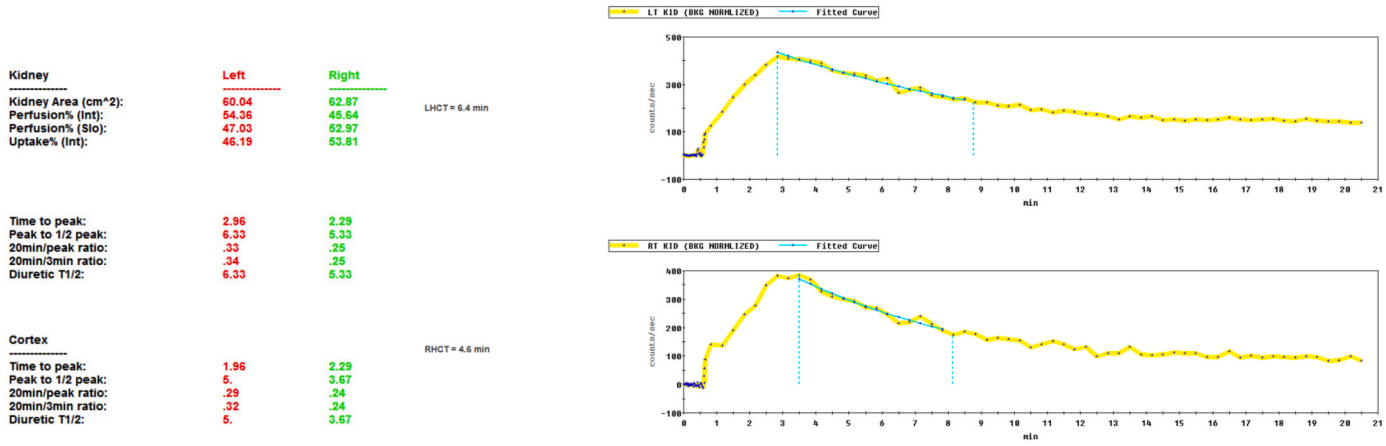

Fig. 4. MAG3 renogram post-treatment demonstrating equivocal split function with 46 % uptake in the left kidney and 53 % uptake in the right kidney. Equal T1/2 lasix clearance times of 6.3 minutes for the left kidney and 5.3 minutes for the right kidney are observed, indicating no functional obstruction.

Table 1
Urological manifestations of IgG4 disease.

Manifestation	Clinical presentation	Investigations	Management
Ureteric thickening	Can mimic UCC; presents with intraluminal obstruction	• CT IVP • FDG-PET • Ureteroscopy with biopsy • Autoimmune screen (Serum IgG4, RF, anti-CCP, C3, C4, anti-dsDNA, anti-Sm, anti-Ro, anti-La, ESR, CRP)	Immunosuppressive therapy (steroids, rituximab) Ureteral stenting or nephrostomy if obstructive uropathy
Retroperitoneal fibrosis	Hydroureteronephrosis with extraluminal obstruction	• MRI/CT abdomen • Retroperitoneal biopsy • Autoimmune screen (see above)	Immunosuppressive therapy (steroids, rituximab) Ureteral stenting or nephrostomy if obstructive uropathy
Interstitial nephritis	Presents with renal dysfunction	• Renal biopsy • Urinalysis • Autoimmune screen (see above)	Immunosuppressive therapy (steroids, rituximab) Renal function monitoring
Prostatitis	LUTS, pelvic pain, prostatic enlargement	• Prostate biopsy • Serum PSA levels • MRI prostate • Autoimmune screen (see above)	Immunosuppressive therapy Antimicrobial therapy (Fluoroquinolones e.g., ciprofloxacin, levofloxacin or trimethoprim-sulfamethoxazole)
Cystitis	LUTS, haematuria	• Cystoscopy with biopsy • Urine cytology • Autoimmune screen (see above)	Immunosuppressive therapy Surveillance cystoscopy

2. Discussion

IgG4-RD is a relatively recently recognized condition with varied clinical manifestations. Urological involvement, though rare, can present diagnostic challenges due to its ability to mimic malignant conditions like ureteric UCC.[5] This case underscores the importance of considering IgG4-RD in patients with unexplained ureteric thickening with non-diagnostic biopsy of urothelial thickening, especially when there is a history of other systemic auto-immune diseases such as rheumatoid arthritis. In this case, the patient's initial presentation with obstructed left kidney and concurrent rheumatoid arthritis flare raised the possibility of an inflammatory or autoimmune aetiology.

The diagnosis of UCC of the ureter relies on combination of imaging (CT IVP or retrograde pyelogram), selective cytology, histopathology and direct visualisation. At least two criteria need to be fulfilled to be diagnostic and this case only fulfilled one criteria. IgG4-RD is characterized by elevated serum IgG4 levels and the infiltration of IgG4-positive plasma cells in various tissues. The diagnosis of IgG4-RD primarily relies on pathological examination, with the following criteria widely accepted: (I) the presence of diffuse or localized masses in one or multiple organs; (II) serum IgG4 concentrations of $\geq$1.35 g/L; and (III) pathological findings of significant lymphocyte and plasma cell infiltration with fibrosis, IgG4-positive plasma cell infiltration, a ratio of IgG4-positive to IgG-positive cells exceeding 40 %, and more than 10 IgG4-positive plasma cells per high-power field (HPF).[6] Meeting all three criteria provides a robust basis for the diagnosis of IgG4-RD. Whilst the pathophysiology of IgG4-RD is still poorly understood, it causes multi-focal and multi-organ calcification and fibrosis in its fibrotic phase that results in secondary manifestations.[7]

The kidney is the genitourinary organ most commonly affected by IgG4-related disease (IgG4-RD). The predominant renal manifestation is IgG4-RD tubulointerstitial nephritis, followed by membranous glomerulonephropathy, and less commonly, obstructive nephropathy involving the renal pelvis, ureter, or retroperitoneum.[8] While involvement of other genitourinary organs such as the ureter, bladder, urethra, and prostate is less common, it can present with variable imaging findings. These findings may include a localized mass within or around the affected organ or diffuse enlargement of the organ (Table 1). Workup for suspected IgG4-RD ureteritis should include serum IgG4 levels, imaging to assess ureteric thickening and lymphadenopathy, and ureteroscopy with biopsy. Accurate diagnosis relies on histopathological confirmation of IgG4-positive plasma cell infiltrate and elevated serum IgG4.

Diagnosing IgG4-related disease (IgG4-RD) based on ureteric biopsy can be challenging, as it may yield inconclusive or inaccurate results. This is due to the often subtle and patchy nature of the pathological features, which may not be captured in limited biopsy samples. In many cases, the definitive diagnosis of IgG4-RD occurs only after a more extensive surgical specimen is obtained, such as during nephroureterectomy, where the characteristic fibrosis, lymphoplasmacytic infiltration, and elevated IgG4-positive plasma cells can be more comprehensively assessed. This aligns with the findings reported by Zhong et al., where a ureteroscopic biopsy suggested atypical urothelium, and the final diagnosis of ureteral IgG4-RD was only made post-

nephroureterectomy, without evidence of cancer.[9]

Management of IgG4-RD involves immunosuppressive therapy with glucocorticoids.[10] Immunosuppressants such as methotrexate, azathioprine, or mycophenolate mofetil can be alternative therapeutic options when IgG4-RD is refractory to glucocorticoid therapy or to avoid long-term use of glucocorticoids.[11] In this case, the patient responded well to methotrexate, prednisolone and rituximab, with significant improvement in serum ESR that corresponded with radiological resolution of left hydroureteronephrosis.

In summary, this case illustrates the diagnostic complexity in distinguishing between IgG4-related disease (IgG4-RD) and urothelial carcinoma (UCC) of the ureter. While CT IVP raised suspicion for UCC, direct visualisation did not reveal the typical appearance of UCC, and cytology and histopathology were non-diagnostic. The presence of low-grade transitional cell carcinoma (LGTa) in the bladder and a history of breast cancer further complicated the diagnostic pathway. Despite these distractions, a high index of suspicion—reinforced by a similar case that led to nephroureterectomy—prompted the consideration of IgG4-RD. Multidisciplinary discussions involving rheumatology and oncology were pivotal in guiding the investigation and treatment, emphasizing the importance of collaboration in complex cases with overlapping features of malignancy and autoimmune diseases. Ultimately, the diagnosis of IgG4-RD was made, highlighting the need for vigilance in considering this condition, particularly in patients with unexplained ureteric thickening and a history of systemic autoimmune diseases.

3. Conclusions

This case highlights the need to consider IgG4-related disease (IgG4-RD) in the differential diagnosis of ureteric malignancies, as its presentation can closely mimic transitional cell carcinoma. Accurate diagnosis relies on elevated serum IgG4 levels and histopathological evidence of IgG4-positive plasma cell infiltration. Given the potential for IgG4-RD to impact multiple genitourinary organs, including the kidney and ureter, a multidisciplinary approach involving urology, radiology, pathology, and rheumatology is crucial for effective diagnosis and treatment. Timely and precise identification of IgG4-RD can prevent unnecessary invasive procedures and ensure appropriate management, ultimately preserving organ function and optimizing patient outcomes.

CRediT authorship contribution statement

David Hennes: Validation, Writing – original draft, Writing – review & editing. **Yuigi Yuminaga:** Conceptualization, Supervision, Writing – review & editing.

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