CASE REPORT

# IgG4-related kidney disease: a rare cause of tubulointerstitial nephritis

Thadathilankal J John[1], Adriano Pellizzon[1], William D Bates[2], Mogamat-Yazied Chothia[1]

*[1]Divisions of General Internal Medicine and Nephrology, Department of Medicine, Stellenbosch University and Tygerberg Hospital, Cape Town, South Africa; [2]Division of Anatomical Pathology, National Health Laboratory Service, Stellenbosch University and Tygerberg Hospital, Cape Town, South Africa.*

## ABSTRACT

A 42-year-old black female was referred with unexplained renal failure. Initial radiological examination revealed a right adnexal inflammatory mass and bilateral hydronephrosis. The renal failure persisted despite the insertion of double J stents. A kidney biopsy showed a lymphoplasmacytic interstitial infiltrate that stained positive for IgG4. A diagnosis of IgG4-related tubulointerstitial nephritis (TIN) with pelvic-limited retroperitoneal fibrosis (RPF) was made and immunosuppressive treatment was initiated, with a good initial response to therapy. This report highlights the importance of considering RPF in cases of unexplained obstructive uropathy and of considering the diagnosis of IgG4-related disease when TIN is found in combination with other organ involvement.

**Keywords:** IgG4-related tubulointerstitial nephritis; retroperitoneal fibrosis; kidney biopsy; immunosuppression.

## BACKGROUND

Acute tubulointerstitial nephritis (TIN) is a common cause of acute kidney injury (AKI) and represents approximately 15% of cases. The most common cause is drugs, particularly beta-lactam antibiotics. Immunoglobulin G4-related renal disease as a cause of AKI is rare and the incidence and prevalence remains unknown. Here we present a case of AKI presenting with unexplained, recurrent obstructive uropathy.

## CASE

A previously well, 42-year-old black female was referred to the Division of Nephrology, with unexplained deterioration in kidney function over a period of 6 months.

Her initial presentation, 6 months prior to the consultation, was that of vague lower abdominal pain. A urinary tract infection was suspected and she was discharged on oral antibiotics. Her kidney function at the time was normal with a serum creatinine concentration (sCr) of 50 µmol/L. Two months later she presented to the gynaecology clinic with similar complaints and it was noted that her kidney function had deteriorated, with sCr rising to 330 µmol/L. An abdominal ultrasound and non-contrasted computed tomography (CT) scan revealed a right adnexal inflammatory mass that crossed the midline, causing bilateral ureteric compression and hydronephrosis. The urologists inserted bilateral double J stents, with improvement in kidney function over a period of a week so that sCr declined to 96 µmol/L. A urology outpatient clinic appointment was arranged, but the patient was lost to follow-up.

Four months later, she presented to the gynaecology clinic with a history of dysuria and urinary frequency. Her kidney function had markedly deteriorated and her sCr had increased to 1557 µmol/L. Her urine volumes were ~1500 mL/day, with no features of volume overload. A repeat non-contrasted CT scan revealed recurrence of the bilateral hydronephrosis despite improvement in the size of the right adnexal inflammatory mass and the

Received 12 January 2017; accepted 17 February 2017.
Correspondence: Dr M-Y Chothia, yaziedc@sun.ac.za.

presence of the double J stents. Also noted was an increase in the size of the para-caval and para-aortic lymphadenopathy.

A urine culture grew a resistant *Escherichia coli* that was successfully treated with ertapenem. Despite adequate antibiotics, replacement of the double J stents and intravenous hydration, there was minimal improvement of her kidney function and persistence of the hydronephrosis. Urine protein excretion at the time was noted to be 2.0 g/day and all investigations for other causes of AKI were negative, including serological tests for systemic lupus erythematosus, hepatitis B and C, syphilis and HIV. No abnormalities were found on serum protein electrophoresis and on testing for urinary Bence-Jones protein. The tumour marker, CA 125, was positive at 87 kU/L (normal range 0–35 kU/L) but this was ascribed to the kidney failure. A kidney biopsy was subsequently performed and revealed a mixed inflammatory infiltrate with lymphoid follicles (Figure 1). Immunohistochemistry showed 20–30 immunoglobulin G (IgG)-positive plasma cells per high-power field (40x), of which more than 50% were positive for IgG4.

Total serum IgG level was increased at 21.0 g/L (normal range 6.5–16.0 g/L). In view of the kidney failure, characteristic histological findings, elevated IgG level and the pelvic inflammatory mass, a diagnosis of IgG4-related TIN with possible pelvic-limited retroperitoneal fibrosis (RPF) was made. The patient was initiated on oral immunosuppression, including azathioprine (150 mg daily) and prednisone at a dose of 1 mg/kg/day (60 mg daily). The prednisone dose was slowly reduced after the first three months. Follow-up of the patient revealed a steady improvement in kidney function (Figure 2).

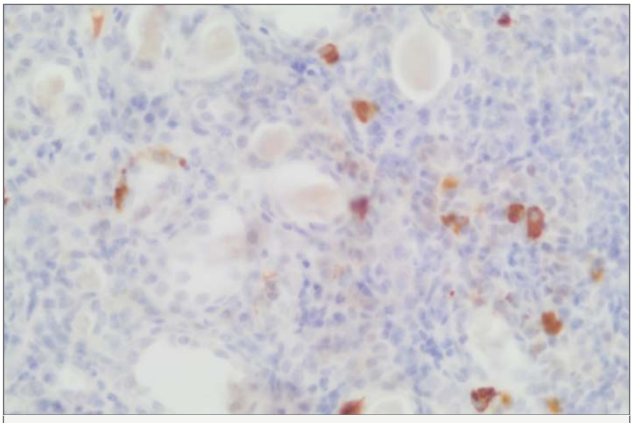

**Figure 1.** An area of inflammatory infiltrate in the interstitium of the kidney biopsy. More than 20 plasma cells per high power field were present and more than 50% of these had positive cytoplasmic staining for IgG4 with an immunohistochemical stain.

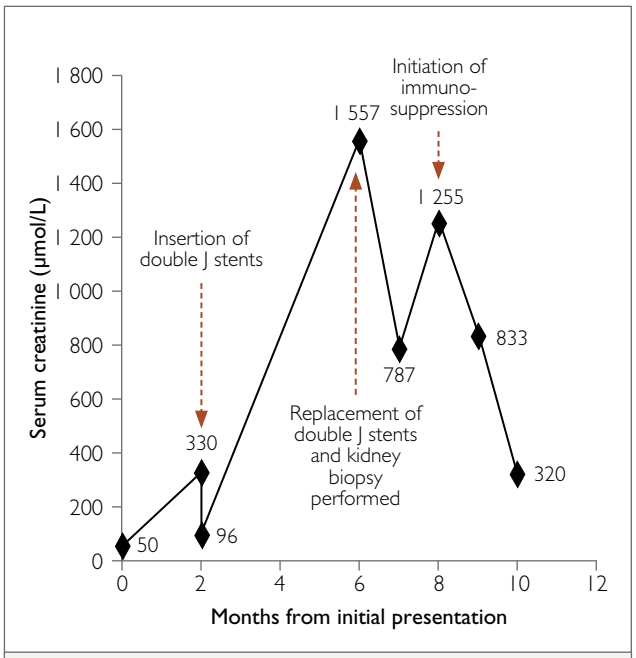


**Figure 2.** Serum creatinine trend since the initial presentation.

## DISCUSSION

Immunoglobulin G4-related disease (IgG4-RD) is a rare, immune-mediated condition of unknown aetiology and comprises various disorders that share clinical, serological and pathological features [1]. These disorders, which were previously thought to be unrelated, include autoimmune pancreatitis, sclerosing cholangitis, inflammatory masses in any organ, sialadenitis, inflammatory aortic aneurysm, lung involvement or retroperitoneal fibrosis. Hallmarks of IgG4-RD include dense lymphoplasmacytic infiltrations with predominant IgG4-positive plasma cells in the affected tissue, usually accompanied by fibrosis and obliterative phlebitis, with increased number of eosinophils [2]. Serum IgG4 levels are typically elevated in about two-thirds of patients. The fibrosis is frequently described as having a "storiform" pattern that resembles the spokes of a cartwheel radiating from the centre [2].

The pathogenesis of IgG4-RD remains poorly understood with both autoimmunity and allergenicity being implicated [3,4]. It is generally more common in middle-aged and older men, particularly in the setting of retroperitoneal fibrosis (RPF) and IgG4-related TIN [5], which is in contrast to our index case. Disease extent and severity, however, appear to be similar in men and women [6].

Making the diagnosis requires a combination of typical clinical findings together with characteristic findings on biopsy of the involved tissue. Our patient was noted to have features of obstructive uropathy. This is a common presentation with 60% to 90% of these cases found to

have multiple organs affected at the time of presentation [7]. TIN is the most commonly described renal manifestation of IgG4-RD [8]. Proposed diagnostic criteria include the histological findings of an interstitial infiltrate with >10 IgG4-positive plasma cells per high-power field, with or without tubular basement membrane immune complexes; radiographic findings of small, peripheral cortical nodules or wedge-shaped lesions or diffuse kidney enlargement; increased serum IgG4 or total IgG; and finally, evidence of other organ involvement, such as retroperitoneal fibrosis [9]. Although not tested for in our case, patients with TIN are likely to have profound hypocomplementaemia resembling lupus nephritis [1]. Other renal lesions described in a Japanese study include mild mesangial proliferative glomerulonephritis, membranous nephropathy and focal segmental endocapillary hypercellularity [8].

RPF is a known manifestation of IgG4-RD and forms a component of the proposed diagnostic criteria [5,9]. In the abdomen, it typically affects the retroperitoneal structures such as the great vessels and ureters. However, atypical abdominal sites include the peritoneal cavity as well as the pelvic cavity [10]. RPF limited to the pelvis, as in our case, is rare with only 15 cases reported [11]. When the fibrotic process involves the pelvis, it may compress the ureters and cause obstruction, as was demonstrated in this case. The fibrosis may resemble a tumour and therefore mimic a malignancy, which is the most important condition to exclude before making a diagnosis of RPF.

Optimal management of IgG4-related TIN has not been established and currently there are no randomized controlled trials that have evaluated treatment [5]. Consensus statements suggest that patients with symptomatic, active disease should receive treatment [12]. Treatment should be initiated with glucocorticoids and, once remission is achieved, certain patients may benefit from maintenance therapy. Our approach was to combine prednisone and azathioprine. This combination has been used successfully in North America, Europe, Korea and China [5]. The simultaneous use of two agents allowed us to wean the prednisone and therefore avoid the adverse effects of long-term glucocorticoid exposure while maintaining adequate immunosuppression. In a case series of 33 patients, the majority of cases were treated exclusively with oral prednisone with treatment responses that varied from partial to complete remission [9]. Our patient had a good initial response to therapy. The natural history of IgG4-related TIN is not well defined, however; the majority of patients relapse and most have a chronic disease process that progresses at a variable rate [13].

## CONCLUSIONS

Our case highlights the importance of always including RPF in the differential diagnosis of unexplained obstructive uropathy. When TIN is found in combination with RPF, or other typical organ involvement, IgG4-related disease should be considered. Although rare, clinicians should be aware of the disease as it may respond to immunosuppressive treatment.

### Conflict of interest

None to declare.

### Ethics approval

Permission for publication was granted by the Stellenbosch University Health Research Ethics Committee (reference number C17/01/001).

## REFERENCES


1. Stone JH, Zen Y, Deshpande V. IgG4-related disease. N Engl J Med. 2012; 366:539-551.
2. Deshpande V, Zen Y, Chan JK, Eunhee EY, Sato Y, Yoshino T, et al. Consensus statement on the pathology of IgG4-related disease. 2012; 25:1181-1192.
3. Cheuk W, Chan JK. IgG4-related sclerosing disease: a critical appraisal of an evolving clinicopathologic entity. Adv Anat Pathol. 2010; 17:303-332.
4. Bateman AC, Deheragoda MG. IgG4-related systemic sclerosing disease–an emerging and under-diagnosed condition. Histopathology. 2009; 55:373-383.
5. Moutsopoulos HM, Fragoulis GE, Stone JH. Overview of IgG4-related disease. In Schur PH, Romain PL, editors. UpToDate. Retrieved 23 February 2017, from http://www.uptodate.com/contents/overview-of-igg4-related-disease.
6. Wallace ZS, Deshpande V, Mattoo H, Mahajan VS, Kulikova M, Pillai S, et al. IgG4-related disease: clinical and laboratory features in one hundred twenty-five patients. Arthritis Rheumatol. 2015; 67:2466-2475.
7. Okazaki K, Uchida K, Koyabu M, Miyoshi H, Takaoka M. Recent advances in the concept and diagnosis of autoimmune pancreatitis and IgG4-related disease. J Gastroenterol. 2011; 46:277-288.
8. Saeki T, Nishi S, Imai N, Ito T, Yamazaki H, Kawano M, et al. Clinicopathological characteristics of patients with IgG4-related tubulointerstitial nephritis. Kidney Int. 2010; 78:1016-1023.
9. Raissian Y, Nasr SH, Larsen CP, Colvin RB, Smyrk TC, Takahashi N, et al. Diagnosis of IgG4-related tubulointerstitial nephritis. J Am Soc Nephrol. 2011; 22:1343-1352.
10. Vivas I, Nicolas AI, Velazquez P, Elduayen B, Fernandez-Villa T, Martinez-Cuesta A. Retroperitoneal fibrosis: typical and atypical manifestations. Br J Radiol. 2000; 73:214-222.
11. Salemis NS, Tsiambas E, Tsohataridis E. Pelvic confined idiopathic retroperitoneal fibrosis mimicking a large tumor. Adv Med Sci. 2009; 54:296-298.
12. Khosroshahi A, Wallace ZS, Crowe JL, Akamizu T, Azumi A, Carruthers MN, et al. International consensus guidance statement on the management and treatment of IgG4-related disease. Arthritis Rheumatol. 2015; 67:1688-1699.
13. Khosroshahi A, Stone JH. Treatment approaches to IgG4-related systemic disease. Curr Opin Rheumatol. 2011; 23:67-71.