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Tubulointerstitial nephritis with hypocomplementemia in IgG4-related kidney disease; a case report and follow-up of a mysterious entity

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ABSTRACT

Idiopathic tubulointerstitial nephritis (TIN) with hypocomplementemia is a rare cause of progressive renal failure, with IgG4-related disease (IgG4-RD) emerging as an important differential diagnosis. Within IgG4-RD spectrum, renal involvement frequently reported however, renal involvement alone is uncommon. We present a case of a 66-year-old male with progressive kidney dysfunction. Clinical evaluation revealed bilateral inguinal adenopathies and laboratory findings showed elevated IgG and IgG subclass 4 levels, along with low-complement. Renal biopsy confirmed extensive TIN with marked lymphoplasmacytic infiltrates and elevated IgG-positive cells, consistent with IgG4-RD. The patient was initiated on glucocorticoid therapy, resulting in partial recovery of renal function. Long-term follow-up demonstrated stable renal function and absence of systemic manifestations of IgG4-RD. This case highlights the importance of considering IgG4-RD in the differential diagnosis of TIN with hypocomplementemia. Glucocorticoids remain the first-line treatment, although alternative regimens may be considered to minimize relapse rate and long-term steroid related toxicity. Timely recognition and management of IgG4-related TIN are essential to prevent irreversible kidney damage and improve long-term outcomes.

Case Report

Implication for health policy/practice/research/medical education:
The description of the rare clinical scenario of renal limited IgG4 disease, management and long-term follow up allows for shared learning experience among clinicians.

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Introduction

Idiopathic tubulointerstitial nephritis (TIN) with hypocomplementemia is a rare cause of progressive renal failure. Among possible etiologies, IgG4-related disease (IgG4-RD) is an important differential diagnosis to consider.

IgG4-RD is a systemic fibroinflammatory disorder that may affect any organ. Renal involvement has been reported in variable frequency 4.5–35% in different series (1), since isolated renal involvement of IgG4-RD is uncommon (2).

Tubulointerstitial nephritis is the most common type of renal involvement, along with membranous glomerulopathy and obstructive nephropathy due to retroperitoneal fibrosis (3).

Case Presentation

We describe a 66-year-old male referred to nephrology due to kidney dysfunction. The patient had a past medical history of hypertension and atrial fibrillation on apixaban. There was no history of nephrotoxic drug use. He had normal renal function on routine exams in the previous year and there was no family history of renal disease.

Serial analytical evaluation revealed progressive renal function deterioration from serum creatinine (sCr) level

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of 1.6 mg/dL in March 2020 reaching a maximum of serum creatinine 5.2 mg/dL in May 2021 without significant proteinuria (protein-creatinine ratio of 0.13), and bland urinary sediment. Renal ultrasound showed 9 cm diameter lobulated kidneys, with normal parenchyma and echogenicity. The patient denied systemic symptoms such as weight loss as well as fever or other symptoms. Clinical examination revealed only painless bilateral inguinal adenopathies. There was no history of cutaneous rash or arthralgia.

Laboratory findings revealed positive anti-nuclear antibody (ANA) at 1/1280, negative double stranded DNA, positive rheumatoid factor, low-complement C3 and C4 with normal C1q. Elevated IgG with elevated subclass IgG1, 3 and 4 was also observed. Serum protein electrophoresis showed polyclonal gammopathy and both urine and serum immunofixations were negative for monoclonal proteins.

Despite slight renal asymmetry, computed tomography angiography excluded renal artery stenosis. Normally differentiated kidney parenchyma was observed, however with emphasised hypodense bilateral renal cortex raising suspicion of infiltrative process. Bilateral inguinal adenopathies (maximum diameter 25×14 mm on the right) were concordant with physical examination. No retroperitoneal masses or other altered aspects were described.

His renal biopsy showed extensive TIN with marked lymphoplasmacytic infiltrates without granulomas. The tubules displayed significant tubulitis, epithelial regenerative changes and foci of basal membrane rupture. Direct immunofluorescence was non-contributory and Congo red staining was negative. Immunostaining displayed the presence of CD138-positive cells and a markedly increased number of IgG and IgG3-positive cells. No storiform fibrosis or vascular changes were observed (Figure 1).

A diagnosis of TIN with hypocomplementemia in the setting of IgG4-related disease was made based on clinical presentation and histopathological findings.

The patient was started on methylprednisolone pulses then switched to 60 mg prednisolone daily from May 21 to June 20, 2021. Steroids were slowly tapered to 5 mg prednisolone and discontinued in August 2022.

During follow-up he partially recovered renal function and maintained stable glomerular filtration rate of 25 mL/min/1.73 m^2. No systemic extra-renal manifestation of IgG-4 disease was made evident during a 29-month follow-up period. Additionally, complement levels remained normal, with C3 at 108 mg/dL and C4 at 9.5 mg/dL (Table 1). As a complication of prolonged steroid treatment, he developed diabetes.

Discussion

We describe a case of IgG4 related TIN treated with glucocorticoids, having partially improved kidney

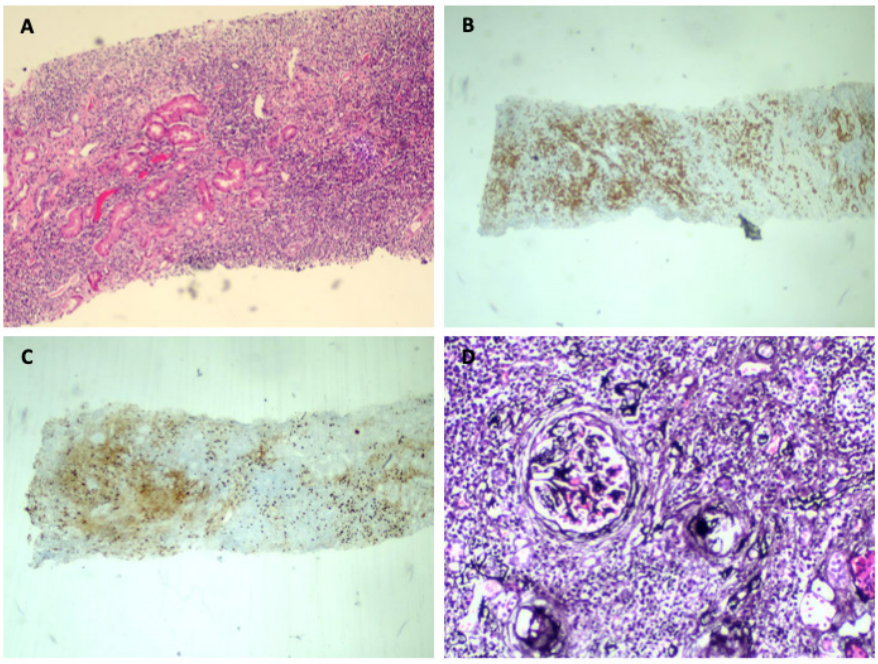

Figure 1. Histopathological findings of renal biopsy. On hematoxylin and eosin staining, an extensive tubulointerstitial nephritis with a dense lymphoplasmacytic interstitial inflammatory infiltrate was found, with associated fibrosis (A - H&E, 100×). B) Immunostaining revealed a marked increase of both IgG-positive (B – IgG, 40×) (IgG, 40×) and IgG4-positive (C – IgG4, 40×) plasma cells present in this infiltrate. Jones methenamine silver staining highlighted intersticial fibrosis and thickening of the Bowman' capsule (D - JMS, 200×).

Table 1. Clinical and analytical findings during follow-up period

Follow-Up	Admission (05/2021)	04/2022	03/2023	10/2023	01/2024
Months	0	11	22	29	**32**
Symptoms					
	None	None	Arthralgia of extremities	None	None
Analytical findings					
Hemoglobin (g/dL)	10.2	12.8	13.9	14.9	
Sedimentation rate (mm/H)		13		21	26
Serum creatinine (mg/dL)	5.2	2.96	2.65	2.90	2.70
GFR (mL/min/1.73 m²)	11	22	26	23	25
Protein/Creatinine ratio	0,13	0.15	0.15	0.23	0.15
Urinary sediment	Normal	Normal	Normal	Normal	
ANA	1/1280		1/160		1/320
Anti-dsDNA	(-)		(-)		(-)
Rheumatoid factor (UI/mL)	18.5 (+)		24 (+)		<9.2 (N)
C3/C4 (mg/dL)	70.3 (↓) / 6.5 (↓)	108 / 24	140 /23	90 / 8.4	108 / 9.5
C1q (mg/dL)	19.7				
Immunoglobulins					
IgG	(↑) 3270				1690 (↑)
Subclass 1	2590 (↑)				1080 (↑)
2	362				335
3	260 (↑)				141 (↑)
4	742 (↑)				232 (↑)
IgA	173				121
IgM	113				89
SPEP	Polyclonal gammopathy				
UPEP	Normal				
Serum immunofixation	Negative				
Treatment					
	Pulse MPD + PDN 60 mg/d for 6 weeks + slow tapper	Low dose PDN. Stopped on 08/2022		None	None

Hb, Hemoglobin; GFR, Glomerular filtration rate, calculated by the CKD-Epi 2021 formula; ANA, Antinuclear antibodies; Anti-dsDNA, anti-double stranded DNA antibodies; SPEP, Serum protein electrophoresis; UPEP, Urinary protein electrophoresis; MPD, methylprednisolone; PDN, prednisolone.

function and maintained a stable kidney function at 29 months.

Few cases of isolated IgG4-related TIN with hypocomplementemia have been described over the past years. These include mostly male patients, over 60 years of age and with serum creatinine >4.1 mg/dL at the time of diagnosis, bland urinary sediment and variable degree of proteinuria (1,4,5). Although presentation may be of rapidly progressive kidney failure, more indolent progression has also been described.

Extensive lymphoplasmacytic infiltrate on renal biopsy is often described in association with low complement, particularly C4. Monitoring complement levels has been considered a helpful indicator of disease activity in IgG4-RD with renal involvement, particularly in relapse monitoring (6).

IgG-4 positive plasma cells may be seen in other autoimmune disorders including lupus nephritis, Sjögren's or ANCA associated vasculitis. However in such scenarios IgG4/IgG-positive plasma cell ratio is usually not high. Differential diagnosis is essential as underlying etiology will ultimately define therapeutic plan (1,2).

Previously reported cases of idiopathic TIN with low complement before the recognition of IgG4-RD, are now thought to be IgG4 related TIN, within the IgG4-RD spectrum. During follow-up period our patient maintained stable renal function and did not demonstrate systemic manifestations compatible with IgG4-RD.

TIN is among IgG4-related disease manifestations in which urgent treatment is warranted due to risk of progression to irreversible kidney damage. Steroids represent first line treatment based on consistent reports of steroid sensitivity. Therefore, most cases are managed with prednisolone with subsequent lowering of serum creatinine levels (6). High relapse rates have been described. Some cases have been reported to be managed with other regimens such as rituximab, mycophenolate mofetil MMF and cyclophosphamide (7). Trials with both MMF and cyclophosphamide point to lower relapse rate compared to glucocorticoids alone (6,8,9). Although specific evaluation in renal IgG4-RD is lacking, anti-CD20 agent rituximab has a better safety profile and has reported to improve renal function reversing renal lesions even in the absence of steroids (10). Use of combined therapy protocol has also been proposed with favourable 4-year follow-up results (11).

Avoiding long term glucocorticoid toxicity is essential, as these patients are likely to require repeated regimens. Our patient had extensive tubular damaged and partially recovered renal function after steroid treatment. As a treatment complication he developed steroid associated diabetes mellitus. Glucocorticoid sparing regimen such as rituximab will be considered if further treatment is deemed necessary.

Conclusion

In summary, we report a rare case of isolated IgG4-related TIN with hypocomplementemia, managed effectively with glucocorticoids, leading to partial improvement and stable kidney function over a long follow-up period. Given the chronic nature of IgG4-RD and potential for relapse, glucocorticoid-sparing therapies offer promising alternatives to mitigate long-term steroid toxicity. Monitoring complement levels and renal function may allow for detection of relapse and treatment optimization.

Authors' contribution

Conceptualization: Vitória Paes de Faria.
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Supervision: Susana Pereira, Maria Clara Almeida.
Validation: Susana Pereira, Maria Clara Almeida.
Writing–original draft: Vitória Paes de Faria, David João.
Writing–review & editing: Rute Carmo, Ana Marta Gomes.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

This case report was conducted in accordance with the World Medical Association Declaration of Helsinki. The patient provided written informed consent for publication as a case report. Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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References

1. Jeong HJ, Shin SJ, Lim BJ. Overview of IgG4-Related Tubulointerstitial Nephritis and Its Mimickers. J Pathol Transl Med. 2016;50:26-36. doi: 10.4132/jptm.2015.11.09.
2. Salvadori M, Tsalouchos A. Immunoglobulin G4-related kidney diseases: An updated review. World J Nephrol. 2018;7:29-40. doi: 10.5527/wjn.v7.i1.29.
3. 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;22:1343-52. doi: 10.1681/ASN.2011010062.
4. Penning A, Kassakian C, Houghton DC, Andeen NK. Hypocomplementemic interstitial nephritis with long-term follow-up. J Clin Nephrol. 2019; 3: 042-045. doi: 10.29328/journal.jcn.1001024
5. 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;78:1016-23. doi: 10.1038/ki.2010.271.
6. Khosroshahi A, Wallace ZS, Crowe JL, Akamizu T, Azumi A, Carruthers MN, et al; Second International Symposium on IgG4-Related Disease. International Consensus Guidance Statement on the Management and Treatment of IgG4-Related Disease. Arthritis Rheumatol. 2015;67:1688-99. doi: 10.1002/art.39132.
7. Capecchi R, Giannese D, Moriconi D, Bonadio AG, Pratesi F, Croia C, et al. Renal Involvement in IgG4-Related Disease: From Sunlight to Twilight. Front Med (Lausanne). 2021;8:635706. doi: 10.3389/fmed.2021.635706.
8. Yunyun F, Yu P, Panpan Z, Xia Z, Linyi P, Jiaxin Z, et al. Efficacy and safety of low dose Mycophenolate mofetil treatment for immunoglobulin G4-related disease: a randomized clinical trial. Rheumatology (Oxford). 2019 Jan 1;58:52-60. doi: 10.1093/rheumatology/key227.
9. Yunyun F, Yu C, Panpan Z, Hua C, Di W, Lidan Z, et al. Efficacy of Cyclophosphamide treatment for immunoglobulin G4-related disease with addition of glucocorticoids. Sci Rep. 2017;7:6195. doi: 10.1038/s41598-017-06520-5.
10. McMahon BA, Novick T, Scheel PJ, Bagnasco S, Atta MG. Rituximab for the Treatment of IgG4-Related

Tubulointerstitial Nephritis: Case Report and Review of the Literature. Medicine (Baltimore). 2015;94:e1366. doi: 10.1097/MD.0000000000001366.
11. Quattrocchio G, Barreca A, Demarchi A, Fenoglio R, Ferro M, Del Vecchio G, et al. Long-term effects of intensive B cell depletion therapy in severe cases of IgG4-related disease with renal involvement. Immunol Res. 2020;68:340-352. doi: 10.1007/s12026-020-09163-3.