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Case Report

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# A Case of IgG4-Related Disease and Membranous Nephropathy Associated with Thrombospondin Type-1 Domain-Containing 7A

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**Keywords**
Membranous glomerulonephritis · Malignancy · tubulointerstitial nephritis · Thrombospondin type-1 domain-containing 7A · IgG4-related disease

**Abstract**
***Background:*** IgG4-related disease (IgG4-RD) is a systemic multi-organ inflammatory disorder which affects the kidney 20% of the time. Patients with intrinsic IgG4-related kidney disease (IgG4-RKD) often have tubulointerstitial nephritis (TIN) whereas glomerular lesions like membranous nephropathy (MN) are less common. Antibodies to thrombospondin type-1 domain-containing 7A (THSD7A) have been described in primary MN, but never in association with IgG4-RKD. ***Case Report:*** We report the first case of IgG4-MN associated with THSD7A antibodies in serum and positivity on glomerular staining, in a 57-year-old Caucasian male with IgG4-RD affecting the pancreas, liver, lacrimal glands, extraocular muscles, and kidneys. This patient presented initially with glomerular disease including significant proteinuria consistent with MN. Glomerular staining for THSD7A antigen and serum THSD7A antibody titres was positive. Treatment with corticosteroids and cyclophosphamide successfully induced remission with resolution of proteinuria, and improvement in renal function. However, despite maintenance azathioprine, the patient relapsed 39 months later. On relapse, there was minimal proteinuria but a significant rise in creatinine. Subsequent renal biopsy showed less glomerular disease and instead a TIN pattern. Subsequent treatment with Rituximab and corticosteroids successfully induced remission. ***Conclusion:*** The role of THSD7A autoantibodies in MN is emerging, and as both IgG4-MN and presence of THSD7A antibody are rare occurrences in themselves, we speculate that there may be an undiscovered association between THSD7A and IgG4-MN. Routine testing for THSD7A in IgG4-MN may help to identify the link.



## Introduction

IgG4-related disease (IgG4-RD) is a rare systemic inflammatory condition with kidney involvement, known as IgG4-related kidney disease (IgG4-RKD), occurring in

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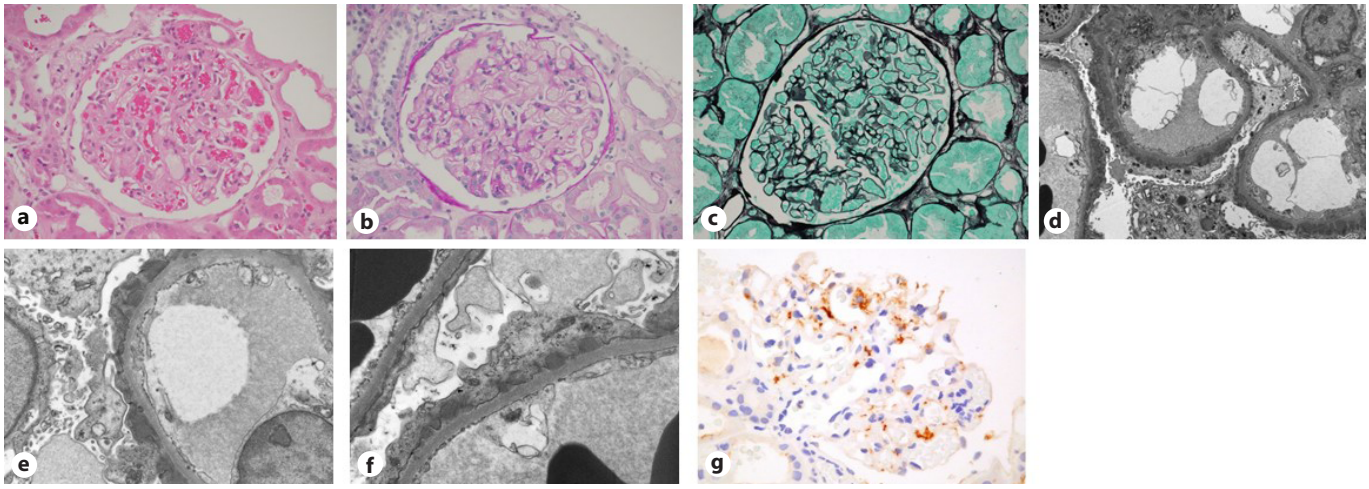

**Fig. 1.** Photographs of the first renal biopsy. **a** H&E staining demonstrating a normal appearing glomerulus. **b** PAS staining demonstrating a normal appearing glomerulus. **c** Silver staining demonstrating no obvious subepithelial spikes. **d–f** Electron microscopy images demonstrating loops with subepithelial deposits consistent with early MN. **g** Immuno-peroxidase staining with THSD7A antigen. H&E, haematoxylin and eosin; PAS, periodic acid-Schiff.

20% of patients [1]. Intrinsic IgG4-RKD includes tubulointerstitial nephritis (IgG4-TIN) reported in 15–24.6% of patients, and membranous nephropathy (IgG4-MN) reported in approximately 7% of patients with IgG4-RKD [1]. IgG4-MN and IgG4-TIN may co-exist or may present in isolation [2].

The kidney is a frequently affected organ in approximately 20% of patients with IgG4-RD [3, 4]. Renal lesions in IgG4-RD are often collectively referred to as IgG4-RKD. The average age of presentation of patients with IgG4-RKD is 65 and 73–87% are men [5, 6]. Patients often present with unexplained renal dysfunction or imaging abnormalities [7]. More than 80% of patients have concurrent extrarenal involvement [6, 7].

Important serological findings in IgG4-RKD include elevated IgG and IgG4 levels and hypocomplementemia [6]. Renal involvement has been associated with hypocomplementemia with more than 50% of patients with IgG4-RKD reporting low levels of complement in the serum [6]. Therefore, C3 and C4 levels may be a suitable biomarker for disease monitoring [8].

Elevated serum IgG4 levels are an important finding in IgG4-RD. While 0–30% of patients with IgG4-RD have normal IgG4 serum levels, elevated IgG4 serum levels are seen in over 90% of patients with IgG4-RKD [6, 9]. Furthermore, serum IgG4 levels dramatically decrease following steroid therapy; however, subsequent raised levels are not necessarily an indication of relapse as raised levels of IgG4 have been reported without apparent relapse [8]. Moreover, IgG4 levels are not specific to IgG4-RD and a normal serum IgG4 level does not necessarily exclude a diagnosis of IgG4-RD [3, 7].

Transmembrane glycoprotein M-type phospholipase A2 receptor 1 ($PLA_2R$) was the first autoantigen recognized in primary MN [10]. In patients with IgG4-MN, serum $PLA_2R$ antibodies are usually negative which can help differentiate primary MN from IgG4-MN [11].

Antibodies to thrombospondin type-1 domain-containing 7A (THSD7A) have since been described in MN, but not in other glomerular diseases or in healthy controls, and several reports suggest a link between THSD7A-associated MN and the development of malignancy [3]. There have been no reported cases of IgG4-MN associated with THSD7A antibodies. We report the first case of IgG4-MN associated with serum THSD7A antibodies in an adult male Caucasian patient.

## Case Report

A 57-year-old man, with asthma diagnosed 20 years previously by a general practitioner, presented to clinic with diarrhoea and weight loss. He was smoking 12 cigarettes a day and was drinking 8 units of alcohol per week. His asthma was well-controlled on inhaled corticosteroids (Beclometasone 200 μg twice daily) and inhaled salbutamol 100 μg when required via metered-dose inhaler. He worked as a baker. Initial investigations included a colonoscopy which was reported as normal and a CT scan of his abdomen demonstrated a pancreatic cyst in keeping with chronic pancreatitis. A surveillance CT scan was arranged to monitor for malignant changes in the cyst.

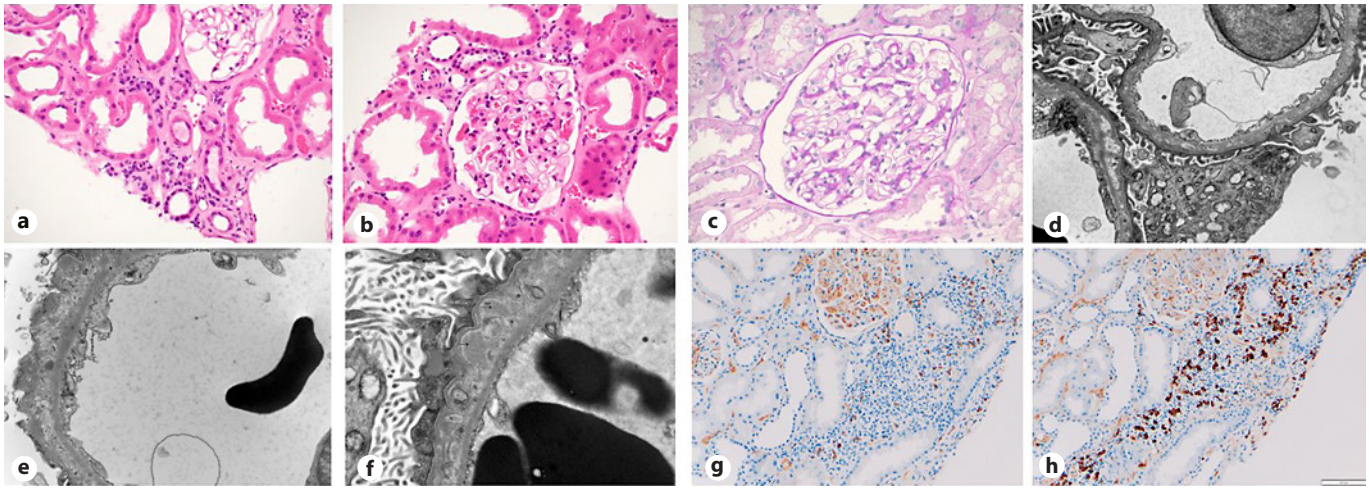


**Fig. 2.** Photographs of the second renal biopsy. **a**, **b** H&E staining demonstrating plasma cell-rich, minimal fibrosis, no storiform fibrosis, acute tubular injury with thin epithelium and nuclear drop-out, and mild mesangial expansion. **c** PAS stain demonstrating mild mesangial expansion without hypercellularity or other abnormal features. **d** Electron microscopy image demonstrating pale areas where the subepithelial deposits were previously, with GBM growing over the deposits creating a circular appearance. **e** Electron microscopy image demonstrating granular deposit material where the subepithelial deposits were seen previously. **f** Electron microscopy image demonstrating dense subepithelial deposits, and microvillous transformation of podocytes. **g** IgG staining demonstrating presence of IgG-positive lymphoid cells. **h** IgG4 staining demonstrating preponderance of IgG4-positive lymphoid cells in comparison to those staining for IgG. H&E, haematoxylin and eosin; PAS, periodic acid-Schiff; GBM, glomerular basement membrane.

Two months later, he developed peripheral oedema and was found to have a urine protein creatinine ratio (uPCR) of 12.5 g/g, serum albumin of 1.1 g/dL, erythrocyte sedimentation rate of 133 mm/1st h, and a C-reactive protein (CRP) of <1 mg/L. A renal biopsy showed features of early MN with subepithelial electron dense deposits on electron microscopy (Fig. 1). A comprehensive autoimmune panel (including anti-$PLA_2R$) was negative, except for a positive rheumatoid factor of 296 IU/mL. Eosinophil count was raised at $0.88 \times 10^{-9}$ cells/L (reference range 0.00–0.40). Further imaging revealed a pancreatic cyst, simple liver cyst, enlarged lacrimal glands, enlarged ocular recti muscles, and striation in the kidneys. Investigations revealed no malignancy. At this stage, he was commenced on doxazosin, furosemide, ramipril, warfarin, human albumin solution 20% (HAS) infusions, and fluid restriction.

He developed diplopia and proptosis of the right eye, and an MRI scan with contrast showed orbital infiltration. Orbital biopsy revealed IgG4-related sclerosing dacryoadenitis and serum IgG4 subclass level was raised at 768 mg/dL. A bone marrow biopsy performed was reported as normal. A diagnosis of IgG4-RD was made as the constellation of symptoms and findings met the 2019 ACR/EULAR classification criteria for IgG4-RD [3].

Treatment with prednisolone and cyclophosphamide induced remission, with successful tapering of prednisolone achieved with azathioprine as maintenance therapy. Renal function stabilized with creatinine of about 1.30–1.47 mg/dL, serum IgG4 subclass level fell to 123 mg/dL, and eosinophil count returned to baseline at $0.03 \times 10^{-9}$ cells/L.

Serum, retrospectively assayed for anti-THSD7A using ELISA, was strongly positive at 2,543 U/mL (reference range <66 U/mL). Anti-THSD7A levels returned to reference range after treatment. The renal biopsy was positive for THSD7A on immuno-peroxidase staining confirming the association with serum antibodies in MN (Fig. 1).

Sixteen months later, he presented with a rise in his creatinine to 2.29 mg/dL and subclinical proteinuria (uPCR 0.743 g/g). During this second presentation, his eosinophil count remained within normal limits. A second renal biopsy showed evidence of resolving MN. In addition, a small area of lymphocytic interstitial inflammation with few plasma cells was present. A small proportion of these cells stained positively for IgG by immunohistochemistry with many more staining positively for IgG4 (shown in Fig. 2). His serum IgG4 subclass level was found to have increased from 286 mg/dL to 593 mg/dL, and serum antibodies to $PLA_2R$ or THSD7A were undetectable during this episode. Remission was achieved with combined prednisolone and rituximab therapy with an improvement in the serum creatinine to 1.69 mg/dL, uPCR to 0.274 g/g, and IgG4 subclass level to 95 mg/dL (Fig. 3).

## Discussion

Types of renal involvement in IgG4 disease have been well reported previously. These are broadly categorized as intrinsic or extrinsic, with IgG4-TIN being the most common pattern of intrinsic kidney disease reported in 15–24.6% of patients with IgG4-RKD, and ureteric obstruction secondary to retroperitoneal fibrosis being a com-

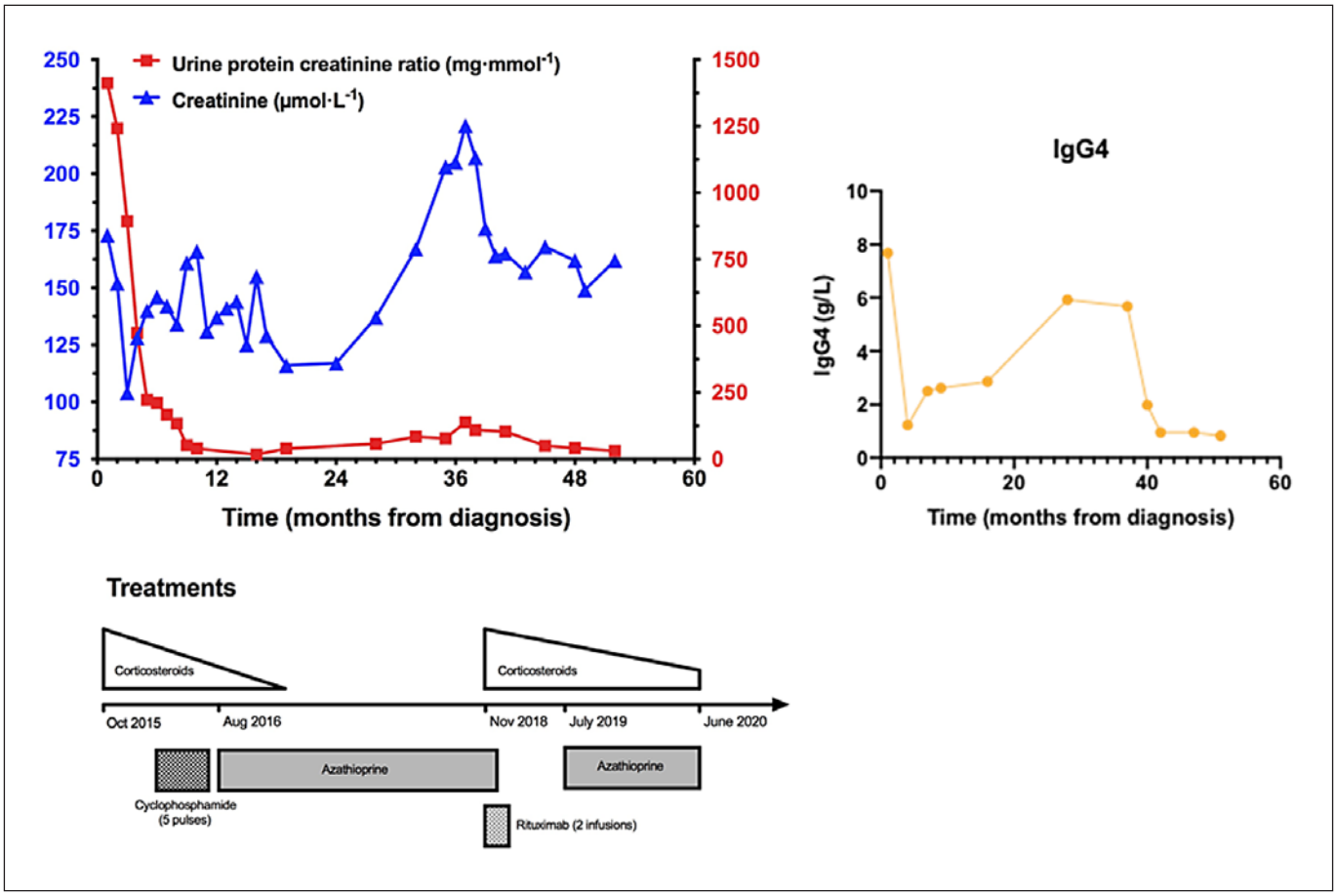


**Fig. 3.** Visual representation of disease activity and management and serum IgG4 subclasses over time from initial diagnosis.

mon form of extrinsic kidney disease [5, 12]. More rarely, IgG4-RKD can manifest as MN. In one study, MN was reported in only 7% of kidney biopsies from patients with IgG4-RKD [1].

IgG4-MN may co-exist together with IgG4-TIN, or it may present in isolation. A study of 9 patients with IgG4-MN found 5 with concurrent IgG4-TIN [2]. The underlying pathogenesis of IgG4-MN has yet to be elucidated, but it may be secondary to immune complex deposition [3]. In this case, proteinuria was the predominant clinical phenotype during the first presentation which is consistent with glomerular disease, and the MN which was seen on renal biopsy. However, interestingly during relapse, there was only mild proteinuria, with a significant rise in creatinine and renal biopsy more consistent with TIN. To our knowledge, this sequence of renal involvement has not been described previously in IgG4-RKD.

Whilst IgG4-RD typically responds to corticosteroid therapy, response to steroid therapy may differ in IgG4-MN, and proteinuria may also persist despite a good response to therapy in other organs [8, 12]. In this case, elevations in serum levels of IgG4 subclass and in urine PCR were seen to correlate with relapse and IgG4 disease activity, suggesting that monitoring of serum IgG4 subclass levels may be beneficial in disease monitoring in patients with IgG4-RD. Furthermore, in this case treatment with corticosteroids and Rituximab was effective in preserving renal function.

The role of THSD7A autoantibodies in MN is emerging. In one study, serum THSD7A autoantibodies were reported in 10% of patients with primary MN negative for PLA2R antibodies [13]. While THSD7A has been found on immunohistochemical analysis in idiopathic and secondary MN, it has not been seen in other glomerular diseases or in healthy controls. Another study found that among 40 patients with confirmed THSD7A-associated MN, 8 went on to develop a malignancy within a median of 3 months [14]. Thus, it has been suggested that there is

a possible link between THSD7A-associated MN and the development of malignancy. However, other reports have suggested that malignancy is the underlying aetiology for some cases of THSD7A-associated MN [15].

The patient described in this case had a diagnosis of asthma, which was well-controlled with low-dose inhaled corticosteroids and bronchodilators; however, raised eosinophils were found on first presentation with IgG4-RKD and THSD7A-associated MN. The association of eosinophilia and THSD7A-associated MN is not clear; however, there have been case reports of THSD7A-associated MN associated with eosinophilia, and severe asthma [16]. Although unlike the previously reported cases of THSD7A-associated MN and eosinophilia, the patient in this case did not have severe refractory asthma [17].

To our knowledge, this is the first reported case of IgG4-MN associated with THSD7A autoantibodies. As THSD7A and its association with MN is an evolving area, screening for antibodies to THSD7A in IgG4-MN could help determine the true incidence of this association and may provide a direct link between these two rare entities. As both IgG4-MN and the presence of anti-THSD7A antibody are rare occurrences in themselves, we speculate that there may be an undiscovered association between THSD7A and IgG4-MN.


## Acknowledgments

We would like to thank the patient and his family for consenting to the publication of this case report.


## Statement of Ethics

The patient and his next-of-kin gave informed consent for publication of the details of this case report with accompanying images. Specific ethical approval was not required.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.


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## Author Contributions

R.M.H. and S.E. performed the literature review and wrote the initial drafts of the manuscript. R.M.H. led subsequent revisions of the manuscript. G.R. is a renal pathologist who provided retrospective reports, and photographs of the renal biopsies, as well as input with the writing of the manuscript. D.A.K.K and B.J.P. were the lead clinicians responsible for the patient and provided guidance and oversight of the writing of the manuscript as well as revisions of the manuscript.

## Data Availability Statement

The data that support these findings are not publicly available as they contain confidential medical information regarding the patient. Further enquiries can be directed to the corresponding author.

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