

## Case Follow-Up: Development of Primary Membranous Glomerulonephritis in a Patient with IgG4 Related Disease

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### Abstract

Renal involvement in immunoglobulin G4-related disease (IgG4-RD) is usually manifested as tubulointerstitial nephritis or secondary membranous glomerulonephritis (MGN). We reported a case of a 28-year-old woman with a history of IgG4-RD who subsequently developed overt nephrotic syndrome. Renal biopsy indicated primary MGN. She was treated conservatively with an angiotensin converting enzyme inhibitor with resolution of her symptoms and paraclinical abnormalities. As far as we know, this is the first report in the literature of co-existing IgG4-RD and primary MGN with phospholipase A2 receptor antibody positivity.

**Keywords:** Glomerulonephritis; Nephrotic Syndrome; IgG; Antibody; Plasma Cells; Enzymes

### Introduction

IgG4-RD is a systemic immune-mediated disease characterized by elevated serum IgG4 levels and three core pathologic findings: storiform fibrosis, obliterative phlebitis, and lymphoplasmacytic infiltrate of predominantly IgG4 positive plasma cells in affected organs [1–3]. Epidemiology data regarding IgG4-RD comes mainly from Japan, reporting 0.28–1.08 new diagnoses per 100,000 population and a prevalence of roughly 8,000 patients (compared to the total country population approximating 130 million people) [4]. However, this is likely underestimated given that IgG4-RD has only recently been recognized as a separate clinical entity and is likely under diagnosed. When IgG4-RD involves the kidneys, it is most often comes in the form of IgG4-tubulointerstitial nephritis. However, cases of MGN secondary to IgG4-RD have been reported, and in the last few years, this has become a known manifestation of IgG4-RD [5]. Only one case of co-existing IgG4-RD and primary MGN exists in the literature, but renal biopsy staining was negative for phospholipase A2 receptor (PLA2R) antibodies [6]. Primary MGN, originally thought to be idiopathic in most cases, is now principally recognized as an organ-specific autoimmune disease, characterized by detection of the PLA2R antibodies [7]. We describe a patient who was diagnosed with IgG4-RD, with subsequent development of lower extremity edema and nephrotic-range proteinuria. Her work-up included a renal biopsy, which was consistent with primary MGN, including staining positive for PLA2R antibodies. As far as we know, our patient represents the first case of IgG4-RD and primary MGN (confirmed with positive PLA2R antibodies) reported in the literature.

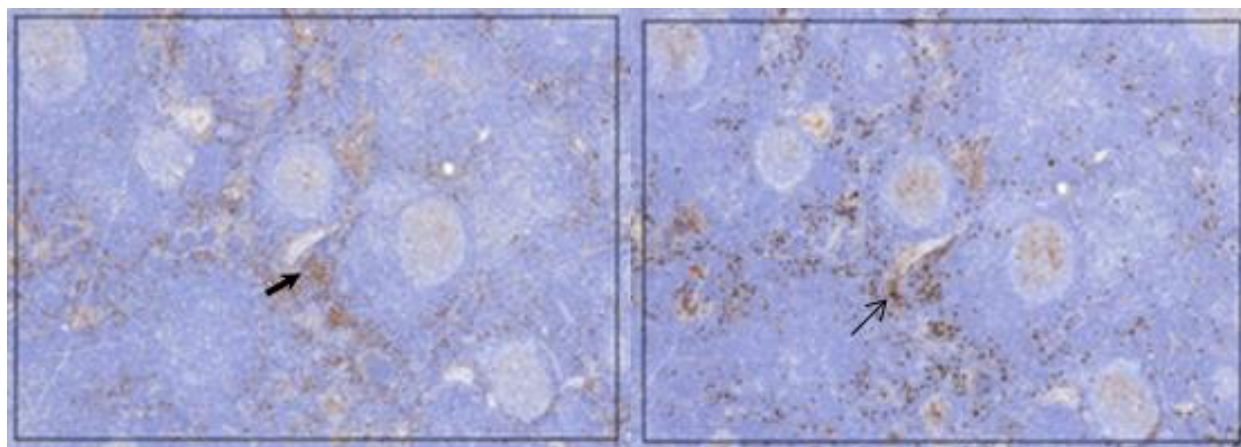
### Case Presentation

In 2012, our institution published the case of a 28 year old African American female with no significant past medical history who presented to her primary care physician with lymphadenopathy, night sweats and fatigue, and was ultimately diagnosed with IgG4-RD [8]. Prior to the diagnosis, she was treated

empirically with a short course of steroids and antibiotics by her primary care provider and experienced a brief remission of her symptoms. The patient's symptoms relapsed weeks later and gradually worsened. Symptom progression prompted additional serologic and radiographic tests, to include imaging with a contrast Computed Tomography (CT) of the neck, chest, abdomen and pelvis. This latter study revealed extensive cervical adenopathy (Figure 1) and hepatosplenomegaly. The patient underwent lymph node resection. She was also evaluated by multiple specialists, to include Oncology, Infectious Disease and then Rheumatology. Table 1 provides a summary of the extensive serologic and tissue examinations that were performed as part of this patient's work-up. Despite a borderline anti-nuclear antibody test at a titer of 1:160, a rheumatologic condition, specifically IgG4-RD, was strongly considered as infection, lymphoma, and other disorders had been excluded based on extensive pathologic, serologic, and imaging studies. An additional lymph node was removed and sent to Pathology for IgG4 staining. This preparation demonstrated an IgG4+/IgG+ cell ratio estimated at 30% (Figure 2), which in combination with the patient's elevated serum IgG4 level of 206 mg/dl (normal 4–86 mg/dl), was highly suspicious for IgG4-RD. The patient was offered therapy with several possible medications, to include glucocorticoids, rituximab and belimumab. While she was educated that typical initial treatment was with glucocorticoids, she declined this therapy due to concerns that this therapy would most likely cause weight gain. Also, despite being presented with B cell depleting or inhibiting medications as possible alternatives



Figure 1: CT Neck with contrast demonstrating lymphadenopathy [8].



**Figure 2:** IgG (left) and IgG4 (right) stains of lymph nodes, 4x magnification. These stains show an IgG4+/IgG+ cell ratio estimated at 30% (thick black arrow = IgG staining, thin black arrow = IgG4 staining)[8].

Pertinent Lab Findings	
Lymphoma	Bone Marrow and Lymph Node Biopsy without evidence of malignancy HTLV 1+2 antibodies (Nonreactive) No monoclonal B-cell, aberrant T-cell or increased blast population on flow cytometry
Multicentric Castleman's Disease	HHV 8 lymph node stains negative HHV 8 IgG and qualitative PCR negative
Autoimmune Lymphoproliferative Syndrome	Less than 1.5% double negative (CD4-CD8-) T Cell count on cytometry
Mycobacterial infection	AFB Culture of lymph node (Negative)
Systemic Lupus Erythematosus	ANA titer (1:160) Anti-dsDNA and anti-Sm antibodies (Negative) Complement levels C3,C4 (within normal range)
Viral Infections	EBV (Nuclear Antigen IgG Positive, Viral Capsid IgG Positive, Viral Capsid IgM Negative, DNA quantitative level <200 copies/ml, negative) CMV (IgM Negative, IgG Negative), Parvovirus B19 (IgM Negative, IgG Negative), Hepatitis (HBs Ag Negative, HBc Ab Negative, HBs Ab Negative, HCV Ab Negative)
Cat Scratch Disease	Bartonella Panel (Negative)
Sjögren's Syndrome	SSA/SSB (Negative)
Fungal infection	Aspergillus niger/fumigatus/flavus Ab (negative) Blastomyces species Ab (negative) Coccidioides immitis Ab (negative) Histoplasma capsulatum yeast/mycelial Ab (negative) Fungal culture of lymph nodes (negative)
Bacterial infection	Aerobic tissue culture of lymph nodes (negative) Anaerobic tissue culture of lymph nodes (negative)

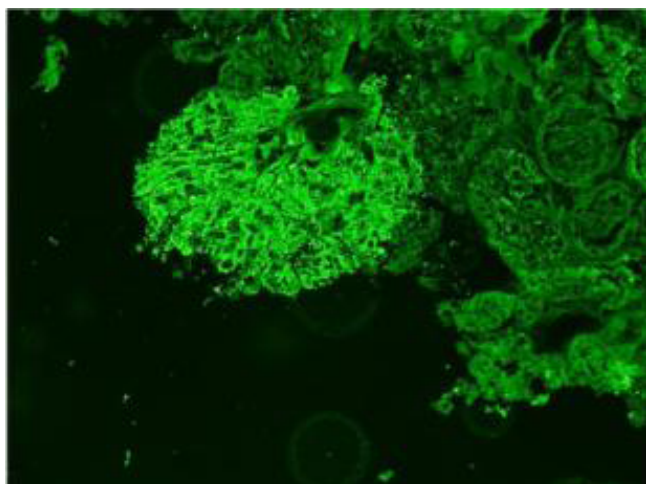
**Table 1:** Differential Diagnosis with Pertinent Lab Findings\*. (Key: \* - HTLV 1+2 = human T-lymphotropic virus type I and II, HHV 8 = human herpes virus 8, IgG = Immunoglobulin G, PCR = Polymerase chain reaction, AFB = acid-fast bacilli, ANA = antinuclear antibodies, anti-dsDNA = anti-double-stranded DNA, anti-Sm = anti-Smith, EBV = Epstein-Barr Virus, IgM = Immunoglobulin M, CMV = cytomegalovirus, HBs Ag = Hepatitis B surface Antigen, HBc Ab = Hepatitis B core antibody IgG, HBs Ag = Hepatitis B surface antigen, HBc Ab = Hepatitis B core antibody, Hbs Ab = Hepatitis B surface antibody, HCV Ab = Hepatitis C virus antibody, SSA = anti-Ro/SSA antibodies, SSB = anti-La/SSB antibodies)

to typical therapy with glucocorticoids, she eventually declined all therapy for a year as she was then considering pregnancy. One year after her diagnosis of IgG4-RD, she presented to the rheumatology clinic with new onset bilateral lower extremity edema and hypertension. She was found to have nephrotic-range proteinuria, which prompted concern for glomerulonephritis secondary to IgG4-RD. A renal biopsy was obtained (Figure 3 & 4) and revealed MGN with positive immunofluorescence stain for PLA2R antibodies, consistent with primary membranous glomerulonephritis, and not consistent with GN secondary to IgG4-RD [7,9]. The patient was started on an angiotensin converting enzyme inhibitor (ACEi) and as needed diuretics with resolution of her lower extremity edema

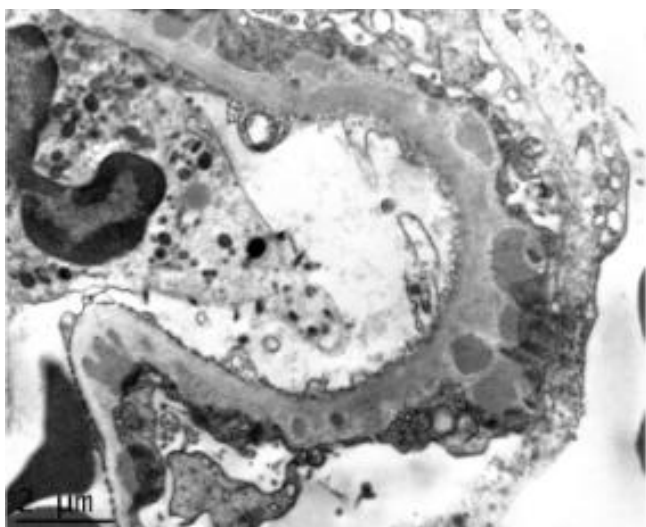
and gradual return of proteinuria to normal limits, which remained normal for duration of follow-up. She eventually sought therapy with rituximab and belimumab, but did not tolerate administration of her first dose of rituximab and had tenuous venous access that repeat infusions of belimumab (after her first infusion) could not be administered. She eventually lost her insurance and follow-up was no longer possible.

## Discussion

IgG4-RD is a relatively new disorder recognized within the last decade. The current diagnostic criteria have been validated [3].



**Figure 3:** Kidney biopsy immunofluorescence staining demonstrating coarsely granular deposits of IgG along capillary loops. C3 and kappa and lambda light chains stained in a similar pattern. Staining for phospholipase A2 receptor was positive.



**Figure 4:** Kidney biopsy electron microscopy demonstrating subepithelial electron dense deposits and diffuse foot process effacement. Features that would suggest secondary MGN include endocapillary proliferation, subendothelial deposits and mesangial proliferation, none of which were present in this biopsy [15].

However, there are speculations about potential improvements in the criteria. These include the concern that normal serum IgG4 levels are present in roughly 50% of patients with IgG4-RD, and that IgG4 plasmablasts may be a more accurate representation of disease activity [10]. As physicians become more aware of the diagnosis of IgG4-RD and more data from IgG4-RD patients is gathered, classification criteria may continue to evolve to become more accurate. With this in mind, we acknowledge that our patient did not meet strict comprehensive diagnostic criteria for IgG4-RD, as the ratio of IgG4+/IgG cells was 30%, not greater than 40% [10]. At the time of the pathology report, storiform fibrosis and obliterative phlebitis were not known characteristic features of IgG4-RD and thus not commented on, but the pathologist did feel that the 'Castleman disease-like, follicular hyperplasia and interfollicular expansion by immunoblasts and plasma cells' was compatible with IgG4-RD due to literature available at the time

[11]. Given the pathology findings, we considered the diagnosis of multicentric Castleman's disease; however several aspects of the patient's serologic evaluation were not consistent with this diagnosis. Negative human herpesvirus-8 testing as shown in table 1 helped to exclude all but Idiopathic Multicentric Castleman's disease. Idiopathic Multicentric Castleman's disease is commonly associated with findings related to IL-6 overproduction, especially anemia, hypergammaglobulinemia and hypoalbuminemia [12]. Our patient had normal hemoglobin (12.3 g/dL), normal albumin (4.3 g/dL), and while her IgG was minimally elevated (due to elevated IgG4), her IgA and IgM levels were normal. Ultimately, IgG4-RD was the best fitting diagnosis given the clinical presentation, laboratory features and histology findings. In addition, one of the key components of diagnosing IgG4-RD is exclusion of the many malignant, infectious and inflammatory disorders that it can mimic. Our patient had a thorough investigation to exclude these alternate diagnoses.

Occasionally, secondary MGN can be diagnosed as a manifestation of IgG4-RD [5]. However, to date, there is only one reported case of co-existing IgG4-RD and primary MGN, albeit in a patient with negative PLA2R antibodies [6]. We acknowledge that this patient may represent the roughly 20% of individuals with primary MGN who test negative for PLA2R antibodies [13]. PLA2R antibodies were originally thought to have a specificity approximating 80% for the diagnosis of primary MGN, but some have cited a specificity now nearing 100% [13]. This, in combination with the kidney biopsy findings and satisfaction of criteria for primary MGN per Kidney Disease Improving Global Outcomes (KDIGO) 2012 guidelines (including exclusion of systemic lupus erythematosus, hepatitis B, drug use, heavy metal exposure, and neoplasia), solidifies our confidence in the diagnosis of primary MGN [14]. Thus, our case illustrates the occurrence of two relatively rare autoimmune diseases, IgG4-RD and primary MGN, occurring simultaneously.

Our patient was treated per 2012 KDIGO guidelines for idiopathic membranous nephropathy. Due to failure to meet any criteria for immunosuppressive therapy, she was treated conservatively with renin-angiotensin inhibition [14]. After addition of an ACEi, her lower extremity edema resolved and her urine protein returned to within normal limits. She did not progress to requiring immunosuppressive therapy due to her primary MGN at the time this article was written, roughly three years after diagnosis. If she had required treatment, given her stable normal renal function, she likely would have been considered for six months of alternating corticosteroids and cyclophosphamide [14]. Despite resolution of her edema and proteinuria, our patient did have intermittent relapses of her IgG4-RD treated with short courses of steroids. She did not tolerate rituximab or belimumab, so it would have been interesting to assess the effect of cyclophosphamide on long-term control of her IgG4-RD. Cyclophosphamide is not routinely used in IgG4-RD, however, there has been a case report of successfully using cyclophosphamide in IgG4-RD to prevent relapse [15]. If administered with alternating corticosteroids, which are considered first line therapy for IgG4-RD, the results would have been confounded [2]. Our patient lost her insurance and moved out of state before any more additional therapies were attempted.

IgG4-RD is an entity that continues to evolve with each passing year. It is possible that primary MGN may represent an unknown manifestation of IgG4-RD. Just years ago, tubulointerstitial nephritis was thought to be the only significant renal manifestation of IgG4-RD. The interim patient data now recognizes secondary MGN as a significant manifestation of IgG4-RD [5]. It seems plausible to think that IgG4-RD and primary MGN may be related, especially given the fact that IgG4 is the predominant PLA2R

subclass of antibodies [11]. However, recent data demonstrates a lack of association between IgG4-RD and PLA2R antibodies [8]. This suggests that despite a common immunoglobulin subclass, the pathophysiology of primary MGN is dissimilar from IgG4-RD. Early evidence suggests pathophysiology is indeed different, as PLA2R antibodies may activate the lectin complement pathway, as opposed to the lymphoplasmacytic infiltration and fibrosis seen with IgG4-RD [2,16]. In addition, elevated levels of IgG4 and PLA2R antibodies in serum can be found in IgG4-RD and primary MGN respectively, but only serum elevations in PLA2R antibodies have been closely associated with disease activity [16]. The association between PLA2R antibodies and disease activity may be due to the direct damaging effect of PLA2R antibodies on their end target, the podocyte. In contrast, the lack of correlation between IgG4 levels and IgG4-RD disease activity argues that IgG4 itself doesn't trigger end organ damage, but that another hit, such as an inappropriate immune response to IgG4, results in the end organ damage. The recent discovery of an association between PLA2R antibodies and human leukocyte antigen DQA1 alleles may shed more light on the pathogenesis of primary MGN, and help distinguish it from other diseases involving IgG4, including IgG4-RD [16]. While our patient could potentially represent another manifestation of IgG4-RD that will become more common in the literature as the sample size of IgG4-RD patients continues to grow, it appears more likely that our patient may represent a rare co-occurrence of two isolated diseases, primary MGN and IgG4-RD.

## Conflicts of Interest

Authors declared no conflicts of interests.

## Disclaimer

The views expressed in this article are those of the authors and do not reflect the official policy or position of the United States Air Force, Department of Defense, or the US Government.

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