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## The coexistence of membranous glomerulonephritis and its cause in the same biopsy: the two faces of IgG4-related kidney disease

Francesco Fortarezza<sup>1\*</sup>, Michele Rossini<sup>2</sup>, Maria Grazia Fiore<sup>1</sup>, Domenico Piscitelli<sup>1</sup>, Loreto Gesualdo<sup>2</sup>, Leonardo Resta<sup>1</sup>, Roberta Rossi<sup>1</sup>

<sup>1</sup>Department of Emergency and Organ Transplantation, Pathology Division, Medical School, University of Bari, Bari, Italy

<sup>2</sup>Department of Emergency and Organ Transplantation, Nephrology Division, Medical School, University of Bari, Bari, Italy

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### ABSTRACT

IgG4-related disease (IgG4-RD) is a systemic immune-mediated disease characterized by fibroinflammatory tumor-like masses that show the peculiar morphological features of storiform fibrosis, lymphoplasmacytic infiltrates rich in IgG4 positive plasma cells and obliterans phlebitis. The disease affects virtually any organ or apparatus and is often associated with increased serum IgG4 levels. Many previously described conditions (e.g. autoimmune pancreatitis, Mikulicz's syndrome, Küttner's tumor, and Riedel's thyroiditis) are now classified to be part of IgG4-RD with the characteristic clinic, serologic and pathologic features. The kidney represents an important target-organ of the disease, mainly as tubulointerstitial nephritis (TIN). Nevertheless, some cases of glomerular disease, especially membranous glomerulonephritis (MNG), have been described in IgG4-related TIN. We report a case of IgG4-related kidney disease in which the two pathological patterns, TIN and MNG, were observed simultaneously in the same biopsy.

### Implication for health policy/practice/research/medical education:

The membranous glomerulonephritis is one of the clinicopathological manifestations of the IgG4-related kidney disease.

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### Introduction

IgG4-related disease (IgG4-RD) is a recently described systemic immune-mediated disease. It can affect nearly any organ or apparatus and arises as pseudo-tumoral mass, often associated with increased serum IgG4 levels. Renal involvement by IgG4-RD is usually represented by an IgG4-related tubulo-interstitial nephritis (TIN) but cases of glomerular disease, especially membranous glomerulonephritis (MNG), have been reported in some case series of IgG4-related TIN (1).

### Case Presentation

We reported the case of a 28-year-old man with a nephrotic syndrome. Five years before, after an antibiotic-resistant fever, the patient underwent a contrast-enhanced computed tomography (CT) that showed a bilateral

thickening of the pulmonary parenchyma, thoracic and iliac lymphadenopathies, mild splenomegaly and hepatomegaly. Left kidney showed a dense, inhomogeneous tissue in the periureteral area, extending down into the pelvic excavation. A systemic infection was clinically hypothesized. Since the urinary obstruction, surgery was performed and the histopathological examination (performed in another hospital) confirmed the clinical diagnosis of retroperitoneal abscess. The family history was unremarkable. The physical examination was negative except for a mild lower extremity edema. Blood pressure was 145/85 mm Hg. The laboratory tests showed the following findings: serum creatinine of 1.16 mg/dL, urine protein; 680 mg/dL (12.71 g/24 h), urine creatinine; 168 mg/dL, hypoalbuminemia (1.6 g/L) and albuminuria. Serological evaluation revealed no evidence of monoclonal

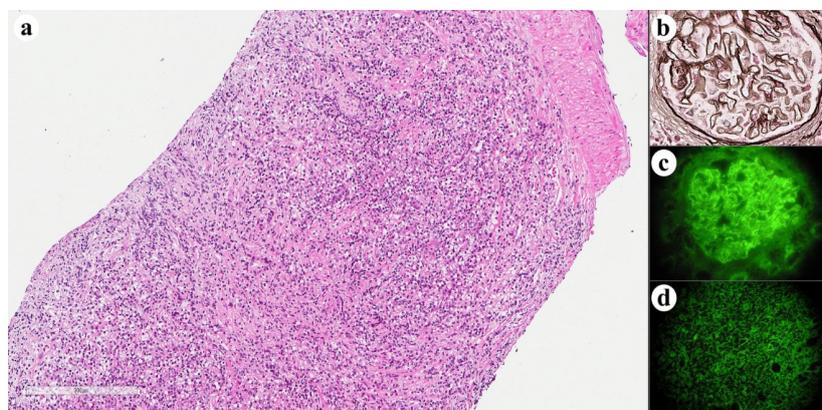
\*Corresponding author: Francesco Fortarezza,  
Email: francescofortarezza.md@gmail.com

protein, anti-neutrophil cytoplasmic antibodies (ANCA), anti-nuclear antibody (ANA), anti-Sjögren's-syndrome-related antigen A (anti-SSA) nor anti-La/Sjögren's syndrome B antigen (anti-SSB) antibodies. Autoantibodies against the phospholipase A2 receptor 1 (PLA2R) were also negative. The immunoglobulin subpopulation showed elevated IgG4 at 895 mg/dL (IgG4 to total IgG ratio of 50.5%), with normal other IgG subclasses, IgE, IgA, and IgD. Therefore, a lymphoproliferative disorder was investigated. The positron emission tomography (PET) scan found hypercaptation in the left kidney, hypermetabolic lymphadenopathies in the left para-aortic, left peri-renal, retro-caval and inter-aortocaval area. Abdominal magnetic resonance imaging (MRI) was suspicious for a lymphoproliferative process of the left kidney. Thus, a percutaneous renal biopsy was performed. The microscopic examination showed a renal cortical parenchyma containing up to 14 glomeruli, 5 of which globally sclerotic. The glomeruli showed a marked thickening of Bowman's capsule and the glomerular basement membrane (GBM). The interstitial compartment was replaced by a dense inflammatory infiltrate consisting of lymphocytes, eosinophilic granulocytes and numerous plasma cells with subversion of the parenchymal architecture and tubular atrophy (Figure 1a). Several fibrotic areas were also evident as a result of collagen deposition with the appearance of "storiform" pattern, typified by a cartwheel appearance of the arranged fibroblasts and the inflammatory cells. The methenamine silver showed subepithelial spikes of the GBM (Figure 1b), moreover highlighted the periglomerular fibrosis and the remnants of tubular basement membrane (TBM). At the immunofluorescence granular and diffuse glomerular and interstitial deposits of polyclonal IgG (3+) and C3 (3+) were evident (Figures 1c-d). The same deposits were also

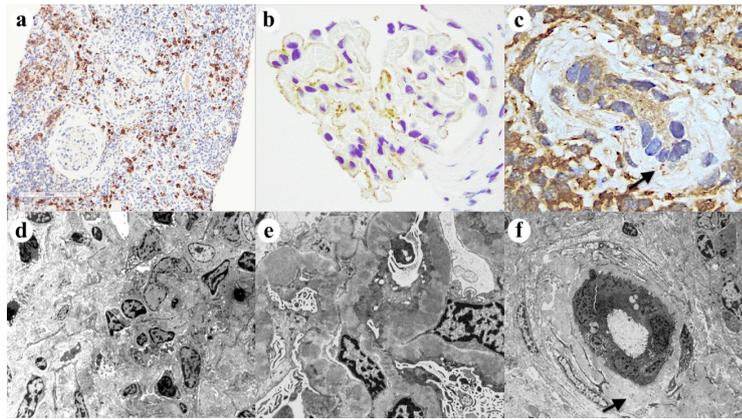
evident in some tubular basement membrane. The staining for PLA2R was negative. The immunophenotypization of the inflammatory infiltrate highlighted B (CD20+) and T (CD3+) lymphocytes organized in primary follicles and numerous plasma cells (MUM1/IRF4+), expressing both  $\kappa$  and  $\lambda$  chains. The IgG4 immunostaining showed more than 30 positive plasma cell per high power field (HPF) and an IgG4+/IgG+ ratio over 40% (Figure 2a). The immunohistochemical reaction highlighted also the subepithelial deposits of the GBM and showed a dot-like positivity in some TBM (Figure 2b-c). The electron microscopy showed large, subepithelial electron-dense deposits also in para-mesangial areas (Figure 2e). The tubules presented a marked thickening of the TBM with some scattered and small electron-dense deposits (Figure 2f). In the interstitium, the ultrastructural examination showed thick collagen bands that individually surrounded the inflammatory cells or in small nests (Figure 2d). This morphological feature is typical of IgG4-related fibrosis (i.e. "bird's eye sign"). According to the current consensus (2), the IgG4+ plasma cells count and IgG4+/IgG ratio were diagnostic for IgG4-RD. The diagnosis of IgG4-related TIN and MNG was made. The patient was treated with a combination of prednisone and rituximab. The therapy led to the reduction of proteinuria (0.6 g/24 h) and the serum IgG4 (60 mg/dL).

### Discussion

The IgG4-RD is an immune-mediated disease that leads to the formation of fibro-inflammatory masses often misdiagnosed as neoplastic or infectious processes. IgG4-RD is a clinicopathological entity. Although histopathology is important, a careful correlation with clinical findings is necessary to reach the correct diagnosis. The consensus statement on the pathology of IgG4-RD



**Figure 1.** The interstitium is replaced by a dense inflammatory infiltrate composing on plasma cells, lymphocytes and eosinophilic granulocytes. A focus of storiform fibrosis is evident in the center of the field (a, hematoxylin and eosin, original magnification  $\times 100$ ). The silver stain shows the subepithelial spikes and a thickening of GBM (b, methenamine silver, original magnification  $\times 400$ ). The immunofluorescence shows granular and diffuse glomerular and interstitial deposits of IgG (3+) (c, original magnification  $\times 400$ ; d, original magnification  $\times 200$ ).



**Figure 2.** IgG4 immunostaining in the interstitium, GBM and TBM (a, b, c) and the corresponding ultrastructural images (d, e, f). The IgG4+ plasma cells are more than 40/HPF (a, original magnification  $\times 100$ ). In the interstitium, the ultrastructural examination shows thick collagen bands that surrounded the inflammatory cells (d, original magnification  $\times 2200$ ). The IgG4 immunostaining shows several subepithelial deposits in the GMB (b, original magnification  $\times 400$ ), clearly visible at electron microscopy, also in para-mesangial area (e, original magnification  $\times 5600$ ). Some scattered deposits in TBMs, remarkable as dot-like positivity (arrow) at IgG4 immunostaining (c, original magnification  $\times 600$ ), and as small electron dense deposits (arrow) at ultrastructural examination (f, original magnification  $\times 2200$ ).

(2) identifies major and minor histopathological criteria, including the lymphoplasmacytic infiltrates, the storiform fibrosis, the obliterans and non-obliterans phlebitis and the eosinophilia. It defines also the quantitative assessment of IgG4 immunostaining, with different threshold values for organ. Diagnostic criteria for IgG4-related TIN have been proposed and included the combination of histology, serology, imaging and the involvement of another organ (3). The pathogenesis of IgG4-RD is not completely understood. Recent researches attribute to T lymphocytes subclasses a pathogenetic role. Either in blood or in affected tissue of IgG4-RD patients, an oligoclonal expansion of CD4+ T effector memory cells with cytolytic and myeloid features have been found. These lymphocytes secrete pro-fibrotic cytokines (IL-1 $\beta$ , TGF- $\beta$ 1) and would, therefore, be responsible for the fibrotic changes (4). T follicular helper cells (T<sub>fh</sub>) are also increased in IgG4-RD patients (5). T<sub>fh</sub>, via IL-4 and IL-10, facilitate B-cell differentiation in plasma cell and the switching of IgG antibodies to IgG4. The role of the IgG4 remains unclear. The immunoglobulin structural and functional characteristics suggest an anti-inflammatory and tolerance-inducing effect. Since the weak binding capabilities to both C1q and Fc $\gamma$  receptors, IgG4 does not activate the complement through the classical pathway (6). Furthermore, IgG4 forms weaker interchain disulfide bridge (i.e. “Fab arm exchange”) resulting in asymmetrical, bispecific antibodies with two different antigen binding sites, which contributes to its anti-inflammatory activity (7). These findings, associated with the aforementioned emerging role of T lymphocytes, strengthen the hypothesis that the IgG4 does not drive the disease, but it represents an epiphenomenon. This assumption could be in contrast

with the pathogenesis of MGN occurring in the set of IgG4-RD. Indeed, IgG4 is the dominant IgG subclasses in primary MGN as well as in IgG4-related MNG (8). Therefore, it has been hypothesized that IgG4 may play a role in the pathogenesis of IgG4-related MNG (9) but more investigations are needed. Moreover, some authors proposed that the proliferating plasma cells produce autoreactive IgG4 against a not yet identified podocyte antigens as for PLA2R (M-type phospholipase A2 receptor) in primary MNG (10). The IgG4-related MNG can be observed without a TIN (1) when it represents the first manifestation of the disease (11) or if the fibro-inflammatory areas have not been sampled by the biopsy.

The main therapeutic option is a steroid-base therapy. The treatment with rituximab to induce B-cell depletion has yielded promising results (12), as observed in our case. This mechanism confirms the possible central role of the B cells in the pathogenesis of IgG4-RD. Indeed, it is thought that the antigen presentation mediated by autoreactive B cells may be essential to maintain the activated state of the T cell subclasses, responsible for the disease clinicopathological manifestation.

### Conclusion

The main manifestation of the IgG4-related kidney disease is the TIN with the observation of the characteristic pathological features, such as storiform fibrosis and lymphoplasmacytic infiltrate. Growing pieces of evidence highlight that the IgG4-related MNG is a rare manifestation of the disease which may occur with or without TIN and could represent the first manifestation of the disease. More studies are needed to understand the pathological mechanisms of the IgG4-RD, its

peculiar dichotomous manifestation in kidney and the promiscuous role of the IgG4.

#### Authors' contribution

FF prepared the manuscript and the figures; MGF, DP, MR and RR performed morphological evaluation; LG and LR conceived and designed the study and reviewed the manuscript. All authors gave final approval for publication.

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This case was presented by the corresponding author (FF) as a slide seminar during the 31<sup>st</sup> European Congress of Pathology (ECP), 7-11 September 2019, Nice, France.

#### Conflicts of interest

The authors declare no conflicts of interest.

#### Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author. Informed consent was obtained from the patient for publication of the report.

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