Clinical and prognostic factors in patients with IgG4-related kidney disease

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Significance statement:

IgG4-related kidney disease is a major manifestation of IgG4-related disease, a systemic fibro-inflammatory disorder. So far, few studies have described the clinical and prognostic factors associated with IgG4-related kidney disease. Of the existing studies, most have small sample size and limited data on long-term prognosis and treatment options. In this observational cohort study, we studied 101 patients with IgG4-related kidney disease from 35 sites. Our findings showed that age at diagnosis, peak serum creatinine, and serum IgG4 concentration ≥5 g/L were independently associated with severe chronic kidney disease at last follow-up. In addition, the number of organs involved and low complement levels were related to the risk of relapse, while Rituximab used as first-line therapy, seemed to decrease its risk. These findings can be used to better recognize patients at high risk for worse clinical outcomes during IgG4-related kidney disease. [CJASN1]

ABSTRACT

Background:

IgG4-related kidney disease is a major manifestation of IgG4-related disease, a systemic fibro-inflammatory disorder. However, the clinical and prognostic kidney-related factors in patients with IgG4-related kidney disease are insufficiently defined.

Method:[CJASN2]

We conducted an observational cohort study using data from 35 sites in two European countries. Clinical, biological, imaging and histopathological data, treatment modalities, and outcomes were collected from medical records.

Results:

We studied 101 adult patients with IgG4-related disease with a mean follow-up of 37.7±37.4 [CJASN3]months. Of these, 87 patients (86%) were male, and the median[CJASN4] age was 68. Eighty-three patients (82%) had IgG4-related kidney disease confirmed by kidney biopsy, with all biopsies showing tubulointerstitial involvement and 16 showing glomerular lesions. Ninety patients (89%) were treated with corticosteroids and 18 (18%) received Rituximab as first-line therapy. At the last follow-up, the estimated glomerular filtration rate was below 30ml/min/1.73m^2 in 32% of patients; 34 (34%) experienced a relapse, while 12 (13%) had died. By Cox survival analysis, the number of organs involved (HR=1.26, CI 95% [1.01-1.55]), low C3 and C4 concentrations (HR=2.31, CI 95% [1.10-4.85]) were independently associated with a higher risk of relapse, whereas first-line therapy with Rituximab appeared to be protective (HR=0.22, CI 95% [0.06-0.78]). At their last follow-up, 19 patients (18.8%[CJASN5]) had an eGFR ≤30ml/min/1.73m2. Age (OR=1.11, CI 95% [1.03-1.20]), peak serum creatinine (OR=2.74, CI

95% [1.71-5.47]), and serum IgG4 level ≥5g/L (OR=4.46, CI 95% [1.23-19.40]) were independently predictive for severe chronic kidney disease.

Conclusion:

IgG4-related kidney disease predominantly ~~affects~~ affected middle-aged males and manifested~~s~~ as tubulointerstitial nephritis with potential glomerular involvement. Complement consumption and the number of organs involved were associated with a higher relapse rate, whereas first-line therapy with Rituximab ~~appeared to~~was associated with lower ~~its risk~~. Patients with high serum IgG4 concentrations (≥5 g/L) ~~were associated with a~~had more severe kidney disease.

INTRODUCTION

IgG4-related disease (IgG4-RD[CJASN6]) is a systemic fibro-inflammatory disorder that may affect any organ.[1–3] First descriptions of IgG4-RD were reported more than a century ago, yet a unified concept of the disease emerged in the early 2000s.[4,5] Of particular note, this organ involvement is characterized by pseudo-tumoral lesions combining lymphoplasmacytic IgG4 positive rich cell infiltrates and a dense tissue fibrosis, usually described as "storiform." The most typical laboratory findings are the total serum IgG and IgG4 levels increase, though normal IgG4 levels should not rule out the diagnosis.[4,6,7] Recently, an international classification criterion was established to harmonize the IgG4-RD diagnosis.[8]

Kidney involvement in IgG4-RD began to be reported in 2002-2004,[9–11] and affects approximately 30% of patients with IgG4-RD.[12,13] Features of kidney impairment in IgG4-related kidney disease include tubulointerstitial nephritis and glomerular lesions, notably membranous nephropathy[14–16] and macroscopic kidney abnormalities observed by dedicated imaging. So far, few studies from Asia and North America have described the impact of IgG4-RD on the kidney.[12,14,17] Furthermore, data on long-term prognosis, relapses and treatment options is also lacking, with little known about patients in Western Europe.[6] Accordingly, we performed a retrospective observational study to describe the clinical, biological, imaging and histopathological data, as well as treatment modalities and outcomes.

METHODS

Study design and ethical statement

We conducted a multicentric retrospective observational study of patients with IgG4-related kidney disease in 33 French and 2 Belgian Nephrology and Internal Medicine Centers. Data was collected under relevant French guidelines and regulations, with patient non-opposition a prerequisite for data use. The local institutional review board approved the study

as minimal risk research, and according to French law, a declaration of conformity was performed by the French data protection authority (CNIL: 2224949).

Study criteria

IgG4-RD was defined according to the 2019 American College of Rheumatology/European League Against Rheumatism Classification Criteria (ACR/EULAR).[8] However, patients with specific antineutrophil cytoplasmic (ANCA) autoantibodies were included if they met the criteria of IgG4-RD after having ruled out the diagnosis of ANCA-associated vasculitis according to the 2022 ACR/EULAR classification criteria.[18–20] We categorized patients with IgG4-related kidney disease into two groups: 1) patients with IgG4-RD with biopsy-proven kidney involvement and no alternative diagnosis, and 2) patients with established IgG4-RD who displayed kidney failure of no alternative cause and/or proteinuria and/or kidney lesions by computerized tomography scan (CT-scan), 18-FDG positron emission tomography (18-FDG-PET CT-scan) or magnetic resonance imaging (MRI), but who did not undergo a kidney biopsy. We excluded patients with kidney failure due to isolated retroperitoneal fibrosis and patients with missing follow-up data.

Data collection

Clinical, biological, imaging and histopathological data were retrieved from medical records. Demographic data and comorbidities included age, gender, hypertension, diabetes mellitus, body mass index, and other coexisting comorbidities, including chronic kidney disease (CKD), cardiovascular disease, and other relevant past medical history. Laboratory findings included: serum levels of electrolytes, albumin, C-reactive protein, C3 and C4 complement components, IgG, IgA, IgM and IgG subclasses, and positivity for anti-nuclear (AAN[CJASN7]) and ANCA autoantibodies.

Kidney function assessment was established on serial serum creatinine measurements from the diagnosis to the last follow-up (when available) and on analysis of urine protein-to-creatinine ratio (UPCR) and urine red and white blood cell counts. Acute kidney injury (AKI) was scored according to the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for AKI.[21] Proteinuria and nephrotic range proteinuria were defined by urine protein ≥0.3 g/day (UPCR ≥0.3 g/g) and ≥3 g/day (UPCR ≥3 g/g), respectively. The glomerular filtration rate was estimated using the 2008 CKD Epidemiology Collaboration equation.[22]

Radiological findings included CT-scan and TEP-CT-scan results. Histological data were retrieved from initial pathological reports and had: the principal diagnosis, glomerular lesions, tubulointerstitial fibrosis and tubular atrophy, and vascular lesions. When available, the degree of fibrosis and tubulointerstitial inflammatory infiltration by lymphoplasmacytic cells was also recorded with the rate of IgG4(+)/IgG(+) cells and the number of IgG4(+) plasma cells per high-power field.

Treatment and outcomes were also collected, and follow-up data were censored at disease relapse and death. Relapse was defined as a progressive disease or recurrence of clinical symptoms, biological abnormalities, or imaging findings after remission, with or without elevation of the serum IgG4 level.[23–25]

Statistical Analysis

Descriptive statistics were used to summarize the data. Results were reported as median and interquartile range (IQR) for continuous variables and counts and percentages for categorical variables. Multivariable models were built using a conditional backward stepwise variable selection process based upon variable influence in unadjusted analysis. Critical entry and exit p-values were 0.2 and 0.1, respectively. Logistic regression was performed to identify the

possible factors involved in severe CKD (as defined by an eGFR ≤30 mL/min/1.73 m^2) at the last follow-up, while Kaplan-Meier survival curves and Cox proportional hazards models were performed to assess the factors associated with the risk of relapse. Nevertheless, it was preplanned to force clinically relevant variables (age, gender, and corticosteroid treatment) into the final model, determining the risk factors for severe CKD. In addition, correlation and interaction were checked within the last models, as well as the assumption for log-linearity of continuous variables and proportional hazard assumptions for survival models. Data are given as odd ratios (OR, 95%CI) or hazard ratios (HR, 95%CI), as appropriate. Models were built assuming 10% of missing data for the relapse status and eGFR at the last follow-up. If we encountered more missing values, a multiple imputations method was planned.

To assess the robustness of our findings regarding the Rituximab effect, we also performed as sensitivity analysis a propensity score weighting analysis.[26–28] The propensity score was built using logistic regression according to Rituximab associated variable. Covariates included in the model were age, sex, serum IgG4 concentration, corticosteroid therapy and serum peak creatinine. The influence of Rituximab on relapse was then evaluated using overlap propensity score-weighted logistic regression models. According to the reviewer's suggestion, we performed additional sensitivity analyses. First, we assessed the time effect on the relapse outcome by forcing the year of diagnosis in the Cox model. Then, we built a conditional logistic regression model stratified by year of diagnosis and finally, we used a generalized mixed model with the year of diagnosis as a random effect. Statistical analyses were performed using R version 4.2.2 (R Foundation for Statistical Computing) using 'survival,' 'survey,' 'ggstatsplot,'[29] 'lme4,' and 'WeightIt' packages.

RESULTS

Baseline characteristics

We identified 125 patients with a differential diagnosis of IgG4-related kidney disease between January 1, 1997, and December 31, 2019, from 35 sites. Among them, 18 did not fulfill the ACR EULAR 2019 criteria, 4 had isolated retroperitoneal disease and 2 had missing data regarding the treatment and follow-up. Finally, 101 patients with IgG4-related kidney disease were included in our cohort (**Figure 1**). Patients' characteristics are detailed in **Table 1**. The median (IQR) age at diagnosis was 68 (57-76). Most (86%) patients were males. Kidney involvement was one of the presenting features at the diagnosis in 61 (60%) patients and a part of systemic organ involvement in 87 (86%) patients. Extrarenal features included lymphadenopathies (57%), type 1 autoimmune pancreatitis (42%), sialadenitis (36%), lung involvement (28%), and cholangitis (25%). The main striking laboratory findings included polyclonal hypergammaglobulinemia and increased serum IgG4 levels in 94% and 90% of cases. On the other hand, complement levels were decreased in 45% of cases when tested, with a significant proportion of patients also displaying autoimmunity features, including nonspecific ANA or nonspecific ANCA positivity in 36% and 22%, respectively.

Kidney findings

The main kidney features are listed in **Table 2**. Patients presented AKI, AKI-on-CKD and isolated CKD in 51 %, 23% and 14% of cases, respectively. At diagnosis, the median (IQR) serum creatinine level was 2.4 mg/dL (1.6-3.6), corresponding to a median (IQR) eGFR of 25 mL/min/1.73 m² (17-43). Urinary sediment was most often bland. The median (IQR) UPCR was 0.6 g/g (0.2-1.1), but 31% of patients had more than 1 g/g, almost exclusively those with glomerular involvement. Kidney lesions by CT-scan abnormalities were identified in 54 (61%) patients. The imaging findings included bilateral kidney hypertrophy, pseudotumor, and low-

density areas in both renal cortices in 19%, 27% and 25% of cases, respectively. The 18-FDG-PET CT-scan was performed in 64 (63%) patients and revealed hypermetabolic kidney lesions in 24 (38%) cases and extrarenal lesions in 46 (74%) cases.

Overall, 83 (82%) patients underwent a kidney biopsy showing tubulointerstitial involvement in all cases. Additional glomerular lesions were reported in 16 (16%) patients, with membranous nephropathy being the predominant pattern. The presence of tubulointerstitial lymphoplasmacytic infiltrates has been observed in all biopsied patients. IgG4 staining was performed in 72 patients and revealed predominant IgG4(+) plasma cells in all patients. The presence of a dense fibrosis, affecting >50% of the kidney tissue, was also described in 42.2% [CJASN8]of cases, but the so-called "storiform" pattern was rarely addressed (**Table 2, Figure 2**).

Treatment and outcomes

Treatment and outcomes are summarized in **Table 3**. Almost all patients (90%) were treated with corticosteroid therapy with a mean initial dose of 0.8±0.3 mg/kg/day. In addition, 18 patients received Rituximab as first-line therapy following a schema of 1g at day 1 and day 15 in 77% of cases, with around 2 cycles realized (Supplementary Table 1[CJASN9]). After a mean follow-up of 37.7±37.4 [CJASN10]months, 35 (35%) patients relapsed within a median (IQR) of 12 months (8.5-24) for the first relapse. Relapse-free survival analysis is detailed in **Table 4** and **Figure 3**. By multivariable analysis, the number of organs involved (HR=1.26, CI 95% [1.01–1.55]), low C3 and C4 concentrations (HR=2.31, CI 95% [1.10–4.85]) were associated with a higher risk of relapse, while the use of Rituximab as first-line therapy was characterized by a lower risk (HR=0.22, CI 95% [0.06–0.78]) (**Table 4, Figure 3a-c**). Therefore, if the patients who received Rituximab as first-line therapy seemed to have less relapse (22% vs. 37%) and

obtain similar kidney outcomes; the proportion of complications such as death (6.2% vs. 14.5%[CJASN11]) and infections (16.7% [CJASN12]vs. 25%) appeared lower compared to the patient without Rituximab as first-line therapy (Supplemental **Table 1**). After weighting both groups and propensity score, the Rituximab as first-line therapy was still associated with a lower risk of relapse (HR=0.27, CI 95% [0.10–0.77]) (Supplemental **Figure 1-3**). This effect also remains despite considering the year of diagnosis (Supplemental **Table 3**).

At the last follow-up, the eGFR was missing for 9 (9%) patients. Out of the overall cohort, 72 (71%) had CKD characterized by a median eGFR of 45 ml/min/1.73m² (26-68), including 32% with an eGFR ≤30ml/min/1.73m^2. Eleven (12%) patients progressed to end-stage kidney disease and 12 (13%) died. Factors associated with severe CKD at the last follow-up (i.e., an eGFR ≤30 mL/min/1.73 m²) were age (OR=1.07, CI 95% [1.03–1.13]) and peak serum creatinine (OR=2.53, CI 95% [1.67–4.24]), while prolonged corticosteroids duration >12 months (OR=0.30, CI 95% [0.10–0.80]) and cholangitis (OR=0.26, CI 95% [0.06–0.84]) were associated with a lower risk. Using multivariable logistic regression, only age (OR=1.11, CI 95% [1.03–1.20]), peak serum creatinine at diagnosis (OR=2.74, CI 95% [1.71–5.47]), and serum IgG4 concentration ≥5g/L (OR=4.46, CI 95% [1.23–19.40]) remained independently associated with the risk of severe CKD at last follow-up (**Table 5**). Of note, the serum IgG4 level at diagnosis and the IFTA state reported on the kidney biopsy also seemed related to the eGFR at the last follow-up (Supplemental **Figure 4**).

DISCUSSION

The present study represents a large series depicting the spectrum and outcome of patients with intrinsic kidney involvement in the course of IgG4-RD. Patients were included from multiple centers in France and Belgium, and all had a definite diagnosis of IgG4-RD

according to the 2019 American College of Rheumatology/European League Against Rheumatism Classification Criteria.[8] A vast majority had a histological assessment of IgG4-related kidney disease, and most displayed a follow-up that allowed the analysis of treatment response, disease relapse(s), and long-term kidney damage due to IgG4-related kidney disease. Collectively our findings provide further insights into the description and management of IgG4-related kidney disease in patients from Western Europe.

Similarly to IgG4-RD, IgG4-related kidney disease affects middle-aged males and is associated with a remarkable increase in serum IgG4 levels and typical kidney infiltration by polytypic IgG4-expressing plasma cells along with tissue fibrosis.[16] The pathological spectrum of IgG4-related kidney disease includes two significant patterns. IgG4-related tubulointerstitial nephritis is by far the most prevalent, representing all cases in our study, while IgG4-related glomerulonephritis is less common, representing less than 20% of cases, with membranous nephropathy being the most common.[30,31] The spectrum of IgG4-related kidney disease also includes macroscopic kidney lesions that may be identified by different imaging techniques in up to two-thirds of patients.[12,14,32] Various patterns have been described, including nodules, kidney hypertrophy, cortical low-density areas and pseudotumor lesions. Notably, such lesions may be observed without kidney dysfunction, proteinuria, and abnormal urinary sediment.

Interestingly, while IgG4-RD may be either systemic or restricted to a single organ, IgG4-related kidney disease is almost exclusively associated with extrarenal features. Previous reports have underscored the correlation between IgG4 titers and systemic involvement, which is consistent with the high proportion of patients with IgG4-related kidney disease who have an increased serum IgG4 level at diagnosis. Kidney involvement thus represents a part of a systemic disease, and patients with IgG4-related kidney disease should be systematically

assessed for extrarenal lesions. 18-FDG-PET CT-scan may be helpful in these cases to screen for hypermetabolic and sometimes asymptomatic organ involvement. In our series, more than 85% of patients displayed extrarenal hypermetabolic lesions, some of which were not clinically obvious.

Beyond serum IgG4 increase, IgG4-related kidney disease is commonly associated with unspecific immunological findings. Low complement levels are observed in one-third of patients with IgG4-related kidney disease across various studies.[12,14,16] Surprisingly, such results are not reported in patients without kidney involvement. Because IgG4 alone is unlikely to activate the classical complement pathway,[33] multiple hypotheses have been raised to account for complement activation in the course of IgG4-related kidney disease, including the concomitant increase of other IgG subclasses leading to the formation of immune complexes and the activation of complement cascade through the lectin pathway.[34]

One-third of patients also display unspecific ANA positivity,[12,14] and 18% have ANCA positivity. While the ACR/EULAR guidelines consider the presence of anti-PR3 and anti-MPO antibodies as an exclusion criterion for IgG4-RD,[8] most ANCA-positive patients in our series, including those with anti-MPO/PR3 specificity, had a definite diagnosis of IgG4-related kidney disease. Danlos et al. reported 18 patients with a concomitant diagnosis of ANCA-associated vasculitis and IgG4-RD, including 22% with kidney involvement.[35] Noteworthy, none of the patients with IgG4-RD had pauci-immune glomerulonephritis, and none with IgG4-related kidney disease had concomitant extra-capillary glomerulonephritis. Whether patients with ANCA positivity represent a peculiar subset among IgG4-RD remains to be determined.

Almost all patients were treated, with a vast majority who received first-line corticosteroid therapy. Most had a partial-to-complete response, which was consistent with previous reports. Such remarkable corticosteroid therapy efficiency is now considered as a retrospective criterion for the classification of IgG4-RD.[8] Unfortunately, the disease, particularly IgG4-related kidney disease, is burdened by a high risk of relapse, approximately one-third of cases, and a significant risk of long-term organ damage. In our study, 70% and 7% of patients developed CKD and end-stage kidney disease, pointing to the need for an optimal management strategy. In our study, prolonged corticosteroid therapy for at least 12 months was associated with better kidney function at the last follow-up by unadjusted analysis. Such association was not apparent by multivariable analysis, with the peak serum creatinine, age at diagnosis, and serum IgG4 ≥5 g/L as the three independent variables associated with worse kidney outcomes. Our data underscored the need for a prompt and accurate diagnosis and initiation of efficient treatment in IgG4-related kidney disease. Alternative therapies to corticosteroids include Rituximab and other immunosuppressants, such as azathioprine or mycophenolate mofetil. Some authors have also suggested the potential benefit of bortezomib and abatacept in some cases.[36] In our cohort, 37% of patients were administered Rituximab, including 18% as first-line therapy, most often associated with corticosteroids. This may allow faster corticosteroid tapering without affecting kidney outcomes. In addition, this strategy was associated with a significantly lower risk of overall relapse. If the retrospective design cannot assure the control of all confounders, the number of death and infections also seemed reduced in the first-line Rituximab group. Our findings underline the results of the prospective open-label trial conducted by Carruthers and al., which showed that Rituximab could be used as first-line therapy with or without concomitant glucocorticoids with a robust clinical response.[37] However, our results can only be hypothesis-generating and the potential benefit of Rituximab in IgG4-related kidney disease remains to be established by further prospective investigation.

Despite major strengths, our study had several limitations, mainly due to its retrospective design leading to potential confounding factors, missing data, and recall bias. Moreover, using ACR EULAR 2019 criteria for assessing IgG4-RD diagnosis made us exclude patients with possible concomitant IgG4-related kidney disease and ANCA-associated vasculitis or systemic lupus. In addition, different policies in kidney biopsy indication and proteinuria and extrarenal features between the various participating centers have also accounted for potential biases in our study. Most importantly, the low number of patients treated by Rituximab should moderate the potential benefit of its use as a first line-option and underscores the need for further collaborative randomized controlled trials.

In conclusion, IgG4-related kidney disease is a well-recognized entity that affects middle-aged males and predominantly presents as tubulointerstitial nephritis with glomerular involvement in approximately a quarter of patients. The response to corticosteroids is usually favorable, but the disease remains characterized by a high risk of relapse in about one-third of patients and more frequently in patients with CKD. Therefore, tighter monitoring should be maintained for patients with many organs involved and high serum IgG4 levels because of poorer outcomes. Rituximab as first-line therapy appears to reduce the risk of relapse without a signal for harmfulness. Due to the retrospective design of this study, our findings remain hypothesis-generating and should be confirmed in future interventional studies.

AUTHORS CONTRIBUTIONS

MZ designed the study; AC performed data management and analysis; AC and MZ wrote the paper. All co-authors were actively involved in the retrospective identification and recruitment

of patients. All authors participated in the critical writing and approved the final version of the manuscript.

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DISCLOSURES

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SUPPLEMENTAL TABLE OF CONTENTS

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TABLES

Table 1. Demographic, clinical, and laboratory findings*

Variable	Entire cohort n = 101
Demographic data	
Age, years, median (IQR)	68 (57-76)
Male, n (%)	87 (86)
Diagnostic delay, months, median (IQR)	9 (2-20)
Extrarenal involvement, n (%)	87 (86)
Pancreatitis	42 (42)
Retroperitoneal fibrosis	15 (15)
Sialadenitis	36 (36)
Cholangitis	25(25)
Lung	28 (28)
Adenopathy	58 (58)
Aortitis/Periaortis	8 (8)
Orbital	5 (5)
Thyroiditis	3 (3)
Breast	2 (2)
Hypophysitis	1 (1)
Laboratory data	
Serum IgG4 dosage, n (%)	94 (93)
IgG4 concentration, g/L, median (IQR)	5.1 (2.3-9)
IgG4 concentration > 1.35g/L	87 (93)
Serum γ-globulins dosage, n (%)	95 (94)
Concentration, g/L, median (IQR)	23.1 (18.7-29.0)
Hyper-γ-globulinemia, n, (%)	81 (85)
Serum IgG dosage, n (%)	84 (83)
↗ IgG, n (%)	73 (86)
Other serum immunoglobulin dosage, n (%)	71 (70)
↗ IgA, n (%)	13 (18)
↗ IgM, n (%)	4 (6)
Other serum IgG subclasses dosage, n (%)	66 (65)
↗ IgG1, n (%)	29 (44)
↗ IgG2, n (%)	19 (28)
↗ IgG3, n (%)	25 (38)
Serum complement dosage, n (%)	82 (81)
↘ C3 or ↘ C4, n (%)	37 (45)
↘ C3, n (%)	33 (40)
↘ C4, n (%)	32 (39)
ANA dosage, n (%)	97 (96)
Positive, n (%)	35 (36)
ANCA dosage, n (%)	81 (80)
Positive, n (%)	18 (22)
CRP, mg/L, median (IQR)	9 (4.5-37)

*Percentages were calculated out of the number of tested patients

Table 2. Kidney findings*

Variable	Entire cohort n = 101	Tubulointerstitial alone n = 85	Tubulointerstitial and glomerular n = 16
Kidney parameters at presentation			
AKI alone, n (%)	51 (51)	41 (48)	10 (63)
AKI-on-CKD, n (%)	23 (23)	19 (22)	4 (25)
CKD alone, n (%)	14 (14)	14 (17)	0 (0)
Preserved kidney function	13 (13)	11 (13)	2 (13)
Baseline serum creatinine, mg/dL, median (IQR)	1.1 (0.9-1.3)	1.1 (0.9-1.3)	1.1 (0.9-1.3)
Baseline eGFR, mL/min/1.73m², median (IQR)	69 (52-87)	69 (51-82)	68 (54-95)
Peak serum creatinine at diagnosis, mg/dL, median (IQR)	2.4 (1.6-3.6)	2.4 (1.6-3.6)	1.9 (1.5-3.6)
eGFR at diagnosis, mL/min/1.73m², median (IQR)	25 (17-43)	25 (17-43)	29 (17-47)
Urine protein-to-creatinine ratio, g/g, median (IQR)	0.6 (0.2-1.1)	0.39 (0.12-0.9)	4 (2.0-4.7)
Urine protein-to-creatinine ratio > 1 g/g, n (%)	31 (31)	18 (21)	13 (81)
Hematuria, n (%)	27 (27)	16 (19)	11 (69)
Leukocyturia, n (%)	16 (16)	12 (14)	4 (25)
Imaging data			
Kidney CT-scan, n (%)	89 (88)	74 (73)	15 (94)
Kidney lesions, n (%)	54 (61)	45 (61)	9 (89)
Low-density areas in both renal cortices, n (%)	22 (25)	19 (26)	3 (20)
Enlarged kidneys, n (%)	17 (19)	13 (18)	4 (27)
Pseudotumor lesions, n (%)	24 (27)	19 (27)	2 (13)
^{18}FDG-PET CT-scan, n (%)	64 (63)	53 (62)	11 (69)
Positive PET CT-scan, n (%)	55 (86)	46 (87)	9 (82)
Kidney hypermetabolic lesion, n (%)	24 (38)	19 (36)	5 (46)
Extrarenal hypermetabolic lesion, n (%)	46 (74)	40 (76)	6 (55)
Histological findings, n (%)	83 (82)	67 (79)	16 (100)
Glomerulosclerosis, %, mean (SD)	23 (43)	22 (42)	33 (58)
Plasmacytic infiltrate, n (%)	76 (92)	62 (93)	14 (88)
IgG4(+) plasmacytic infiltrate, n (%)[#]	72 (87)	58 (87)	14 (88)
Lymphocytic infiltration, n (%)	77 (93)	63 (94)	14 (88)
Lymphoid follicle formation, n (%)	15 (18)	12 (18)	3 (19)
Eosinophilic infiltration, n (%)	10 (12)	9 (13)	1 (6)
Interstitial Fibrosis and Tubular Atrophy, n (%)	72 (87)	57 (85)	15 (94)
Interstitial Fibrosis and Tubular Atrophy grade (%)			

<10%	7 (8)	7 (10)	0 (0)
[10-25%[	7 (8)	5 (8)	2 (13)
[25-50%[	12 (15)	6 (9)	6 (38)
≥ 50%	35 (42)	29 (43)	6 (38)
Tubulitis, n (%)	32 (39)	26 (39)	6 (38)
Tubular deposits by immunofluorescence, n (%)	22 (27)	17 (25)	5 (31)
Glomerular deposition by immunofluorescence, n (%)	11 (13)	2 (3)	9 (56)

* Percentages were calculated out of the number of tested patients

[#]The IgG4 stain was positive in all kidney biopsies when performed. 4 patients with plasmacytic infiltrate did not have IgG4 staining.

Table 3. Treatment and outcomes

Variable	**Entire cohort** n = 101
First line treatment	
Corticosteroids, n (%)	90 (90)
Initial dose, mg/kg/day, mean (SD)	0.8 (0.3)
Duration ≥ 12 months, n (%)	38 (39)
Rituximab + corticosteroids, n (%)	13 (13)
Rituximab alone, n (%)	5 (5)
Overall treatment	
Corticosteroids, n (%)	90 (90)
Rituximab, n (%)	36 (37)
Azathioprine, n (%)	11 (12)
Mycophenolate mofetil, n (%)	6 (6)
Outcomes	
Follow-up, months, mean (SD)	37.8 (37.4)
Kidney function	
Serum creatinine at last follow-up, mg/dL, median, IQR	1.5 (1.1-2.2)
eGFR at last follow-up, mL/min.1.73m², median, IQR	45 (25-68)
eGFR at last follow-up ≤ 30 mL/min.1.73m², n (%)	29 (32)
End-stage kidney disease, n (%)	11 (12)
Relapses	
Number of relapses, n (%)	35 (35)
Time to relapse, months, median, IQR	12 (9-24)
Complications	48 (55)
Death, n (%)	12 (13)
Diabetes, n (%)	29 (35)
Infection, n (%)	20 (23)

Table 4. Relapse-free survival (cox survival analysis)

	Unadjusted analysis		Multivariable analysis	
	HR	**95%CI**	**HR**	**95%CI**
Number of organs involved	1.29	(1.03-1.60)	1.26	(1.01-1.55)
ANCA positivity	3.18	(1.39-7.31)		
↘ C3 and C4 levels	1.83	(0.90-3.72)	2.31	(1.10-4.85)
Kidney imaging lesions	1.85	(0.89-3.85)		
First-line Rituximab	0.37	(0.12-0.96)	0.22	(0.06-0.78)

Table 5. Covariates associated with eGFR at last follow-up ≤ 30 mL/min/1.73m² (logistic regression)

	Unadjusted analysis		Multivariable analysis	
	OR	**95%CI**	**OR**	
Age	1.07	(1.03-1.13)	1.11	(1.03-1.20)
Cholangitis	0.26	(0.06-0.84)		
Peak serum creatinine	2.53	(1.67-4.24)	2.74	(1.71-5.47)
Serum IgG4 concentration ≥5 g/L	2.34	(0.93-6.22)	4.46	(1.23-19.40)
Corticotherapy >12 months	0.30	(0.10-0.80)	0.37	(0.08-1.43)
Number of organs involved	0.81	(0.58-1.10)		
↘ C3 and C4 levels	0.89	(0.34-2.30)		
First-line Rituximab	1.19	(0.37-3.53)		

FIGURES AND FIGURE LEGENDS

Figure 1. Flow chart

Figure 2. Typical kidney pathology in IgG4-related tubulointerstitial nephritis (IgG4-TIN). (A) Light microscopic kidney biopsy findings in an IgG4-TIN patient with extensive interstitial fibrosis, tubular atrophy, and interstitial inflammation (Trichrome stain, magnification x55, scale bar = 200 μm). **(B)** High power view of lymphoplasmacytic infiltrate within the kidney interstitium with interlacing fibrils of storiform fibrosis (Periodic acid–Schiff stain, magnification x400, scale bar = 20 μm). **(C)** Typical storiform fibrosis in IgG4-TIN (Periodic acid-methenamine silver stain, magnification x200, scale bar = 50 μm). Lymphocytes and plasma cells are encircled by collagenous tissue and diffuse fibrosis. **(D)** Immunohistochemistry for IgG4 showing numerous interstitial IgG4-positive plasma cells (magnification x400, scale bar = 20 μm). Images courtesy of S. Ferlicot, Bicêtre University Hospital, France.

Figure 3. (A-C) Kaplan-Meier survival estimates of relapse-free-survival according to the presence of **(A)** ANCA; **(B)** Complement concentration; **(C)** First-line Rituximab therapy. **(D)** Violin plot of the number of organs involved according to relapse occurrence.