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Clinical Manifestations and Long-term Outcomes of IgG4-Related Kidney and Retroperitoneal Involvement in a United Kingdom IgG4-Related Disease Cohort

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Introduction: IgG4-related disease (IgG4-RD) is a relapsing multisystem fibro-inflammatory disease, which may involve the kidney (IgG4-related kidney disease [IgG4-RKD]) and retroperitoneum (IgG4-related retroperitoneal fibrosis [IgG4-RPF]). The aim of this study was to describe IgG4-RKD and IgG4-RPF in the United Kingdom.

Methods: We conducted a retrospective observational study of patients with IgG4-RKD and IgG4-RPF in a multicenter IgG4-RD cohort. Data were collected through review of medical records. We describe clinical parameters at baseline, histological and radiological findings, treatment, and patient outcomes.

Results: Of 154 patients with IgG4-RD, 14 (9.1%) had IgG4-RKD, 10 (6.5%) had IgG4-RPF, and 4 (2.6%) had both. Patients were aged 58.2 ± 14.2 years, and 26 (92.9%) were male. Creatinine at presentation was worse in those with intrinsic renal disease (229 μmol/l vs. 110 μmol/l; $P = 0.0076$). Serum IgG4 was elevated in the majority of patients (87.5%), and hypocomplementemia was present in half of those with IgG4-RKD. Fifteen patients underwent renal biopsy; tubulointerstitial nephritis with abundant IgG4+ plasma cells was the most common finding (n = 14; 93.3%), and 4 (26.7%) patients had membranous nephropathy. Most patients (89.3%) were treated with corticosteroids, and 4 (16.0%) with additional azathioprine as initial management. Thirteen patients (46.4%) relapsed over 60 ± 48 months of follow-up, at median 18 (12–36) months after renal/RPF diagnosis; 61.5% of relapses were in the kidney. Renal function deteriorated in 5 patients (20.8%), including 2 (8.3%) who reached end-stage renal disease (ESRD).

Conclusion: IgG4-RKD and IgG4-RPF represent major organ manifestations of IgG4-RD, and should be identified early with prompt treatment to prevent progression to ESRD.

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IgG4-RD is a recently recognized multisystem disease characterized by lymphoplasmacytic inflammation and fibrosis in affected tissues.[1,2] It can affect almost any organ system in the body.[3] Renal involvement may manifest as an intrinsic kidney disease (IgG4-RKD) or as a consequence of ureteric obstruction from retroperitoneal fibrosis (IgG4-RPF). Intrinsic kidney disease is most commonly a tubulointerstitial nephritis (IgG4-TIN), but may also present with a variety of glomerular lesions, in particular membranous nephropathy, or through abnormalities on renal imaging such as multiple low-density lesions or diffusely enlarged kidneys.[4,5] Organ-specific diagnostic criteria have been proposed, including Raissian criteria for IgG4-TIN.[6] IgG4-RD is responsive to immunosuppressive therapies, but delays in diagnosis and disease relapse lead to a risk of permanent organ damage including progression to end-stage renal disease (ESRD).[6–8] Early recognition of IgG4-RKD, and its distinction from other multisystem diseases that affect the kidney, is therefore important.

Cohorts of patients with IgG4-RKD and IgG4-RPF have been reported in North America[6,9] and Asia,[7,8,10–14] but

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the features of renal involvement in Europe are yet to be described. We undertook this study to describe the clinical characteristics and outcomes of renal and retroperitoneal involvement in a cohort of IgG4-RD patients from the United Kingdom (UK).

METHODS

Study Design and Setting

We conducted a retrospective observational study of patients with IgG4-RD managed at the John Radcliffe Hospital, Oxford, University College London Hospital, and the Royal Free Hospital, London, UK. These centers provide tertiary care to patients with IgG4-RD, and a prospective London−Oxford database of IgG4-RD patients was established in 2010. The IgG4-RD service was set up by gastroenterologists, with an initial focus on hepatobiliary and pancreatic disease, but now care is provided to patients with multisystem disease by specialists in the full range of organ systems affected by IgG4-RD, including rheumatologists, nephrologists, oral medicine and respiratory physicians, histopathologists, radiologists, and surgeons. Patients with IgG4-RD are referred from local, regional, and national hospitals, and video-linked multidisciplinary team meetings are held every 6 weeks between the London and Oxford groups. Patients with autoimmune pancreatitis, IgG4-sclerosing cholangitis, IgG4-related lung disease, and 1 patient with IgG4-RPF in this cohort have previously been reported.[15–17]

Participants and Definitions

All adult patients (aged >18 years) with a diagnosis of IgG4-RD between 2002 and 2018 in the London−Oxford cohort were included. Diagnosis of IgG4-RD was made according to recognized diagnostic criteria,[18] consensus histological criteria,[19] and/or organ specific diagnostic criteria, as appropriate.[6,20]

Patients were identified with renal and retroperitoneal involvement according to the following definitions: (i) renal involvement (IgG4-RKD): a renal biopsy result consistent with IgG4-RD (IgG4-TIN fulfilling the Raissian criteria,[6] or biopsy-proven membranous nephropathy if IgG4-RD has been diagnosed at another site); or IgG4-RD diagnosed at another organ site and renal imaging consistent with IgG4-RKD (multiple low-density lesions or diffusely enlarged kidneys on computed tomography [CT], or renal uptake on positron emission tomography−computed tomography [PET-CT] without other obvious cause); (ii) retroperitoneal involvement (IgG4-RPF): RPF biopsy consistent with IgG4-RD (according to consensus criteria[19]), or IgG4-RD diagnosed at another site and RPF (periaortic or periureteral) on imaging (with or without ureteric obstruction).

Data Collection

Demographic and clinical data were collected in patients with IgG4-RKD and IgG4-RPF from the London−Oxford database, and by further review of medical records. This included gender, age at diagnosis, medical comorbidities, other IgG4-RD organ involvement, laboratory parameters at presentation, and radiological findings. Renal biopsy results were recorded, including glomerular and tubulointerstitial abnormalities on light microscopy, immunohistochemistry including details of IgG4 staining, and electron microscopy. Fibrosis was characterized as storiform in nature if collagen fibers were radially arranged in a whorled pattern that seemed to weave through the tissue.[1] The opinion of the reporting renal pathologist and/or reviewing pathologist at the specialist IgG4-RD multidisciplinary team was taken to describe histological features. We documented patient management including details of immunosuppression, as well as renal and patient outcomes (response to treatment, relapse, development of ESRD and its management, and mortality) during follow-up. Progressive renal impairment was defined as >15% reduction in estimated glomerular rate (eGFR) from baseline. Complete response in membranous nephropathy was defined as resolution of proteinuria (<300 mg/d, or protein:creatinine <30mg/mmol, or urine dipstick trace or negative for protein). Relapsed IgG4-RD was a clinical diagnosis based on the consensus opinion of the multidisciplinary team (e.g., deterioration in renal function or in liver function tests without other obvious cause in a patient with known IgG4-RKD or IgG4-related hepatobiliary disease, respectively). A structured vignette (Supplementary Table S1) describing presentation, investigation, and management was prepared for each case.

Outcome Measures and Statistical Analysis

We determined the prevalence of renal and retroperitoneal involvement in the London−Oxford cohort. We performed a descriptive analysis of demographic and clinical parameters at baseline, radiology findings, histological findings in patients with IgG4-RKD, treatment, and renal and patient outcomes. Variables are presented as number and percentage, mean and SD, or median and interquartile range (IQR), depending on data distribution. We compared variables in patients with intrinsic renal disease (with or without RPF) to those with RPF (without intrinsic renal disease) using the Student t test and Mann−Whitney test if continuous, and using tests of proportionality (χ^2 or Fisher exact) if categorical. We also compared rates of IgG4-RD relapse and renal outcomes (progressive renal impairment or not) between patients maintained on immunosuppression, and those patients on no or

minimal immunosuppression (prednisolone ≤5 mg/d and no steroid-sparing agent). All analyses were conducted using GraphPad Prism version 7 (https://www.graphpad.com) with a P value <0.05 considered to represent statistical significance.

RESULTS

Prevalence of IgG4-RKD and IgG4-RPF

Of 154 patients with IgG4-RD, 28 patients (18.2%) had renal or retroperitoneal involvement (Figure 1). Fourteen patients (9.1%) had intrinsic renal disease, 10 (6.5%) had RPF, and 4 (2.6%) had both intrinsic renal disease and RPF.

Demographic and Clinical Characteristics at Baseline

Demographic details, basis of renal/RPF involvement, and other IgG4-RD organ involvement are outlined in Table 1. The mean age of the patients with IgG4-RKD and IgG4-RPF was 58.2 ± 14.2 years, and 26 patients (92.9%) were male. In all, 25 patients (89.2%) had other organ involvement of IgG4-RD. A total of 18 patients (64.3%) had comorbid medical disease. Most common comorbidities were hypertension (n = 12, 43%), diabetes mellitus (n = 7, 25%), ischemic heart and cerebrovascular disease (n = 5, 18%), and obstructive airways disease (n = 3, 11%). Either IgG4-RKD or IgG4-RPF was part of the initial presentation of IgG4-RD in 20 patients (71.4%), whereas in the other patients it represented relapsed disease in patients with a pre-existing diagnosis of IgG4-RD.

Laboratory Parameters at Presentation

Laboratory parameters at presentation are outlined in Table 2. Serum IgG and IgG4 levels were elevated in 13 (52%) and 21 (87.5%) patients at diagnosis, respectively. Serum creatinine was higher (229 μmol/l vs. 110 μmol/l, $P = 0.0076$) and eGFR lower (27.9 ml/min per 1.73 m^2 vs. 60.9 ml/min per 1.73 m^2, $P = 0.011$) in patients with intrinsic renal disease compared to those without. Complement C3 or C4 was low in 6 patients (50.0% of those in whom it was measured) with IgG4-RKD.

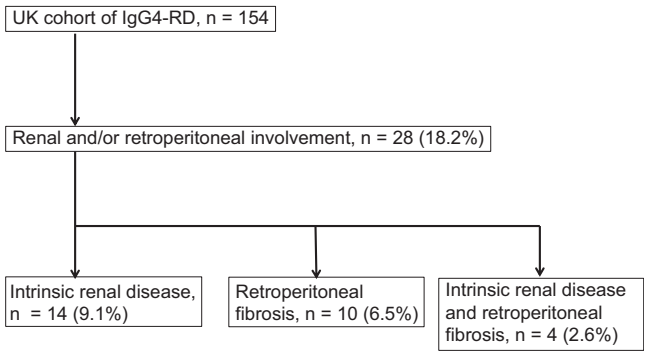

Figure 1. Cohort description.

Table 1. Demographic details, inclusion criteria, and baseline clinical data

Parameter	Entire cohort	Intrinsic renal disease	No intrinsic renal disease	*P* value
Number of patients	28	18	10	
Demographic data				
Age, mean (SD)	58.2 (14.2)	57.0 (12.4)	60.3 (17.6)	0.57
Male, n (%)	26 (92.9)	17 (94.4)	9 (90.0)	0.99
Criteria for renal and RPF involvement[a]				
Renal biopsy consistent with IgG4-RD		13		
IgG4-RD diagnosed at other site and renal imaging abnormalities consistent with IgG4-RD		5		
RPF biopsy consistent with IgG4-RD			4	
IgG4-RD diagnosed at other site and RPF on imaging			6	
Other organ involvement, n (%)[b]				
Pancreas	17 (60.7)	10 (55.6)	7 (70.0)	0.69
Biliary tree	7 (25.0)	6 (33.3)	1 (10.0)	0.36
Liver	3 (10.7)	2 (11.1)	1 (10.0)	0.99
Salivary gland	6 (21.4)	5 (27.8)	1 (10.0)	0.37
Lymph nodes	6 (21.4)	3 (16.6)	3 (30.0)	0.63
Lung	5 (17.9)	2 (11.1)	3 (30.0)	0.32

eGFR, estimated glomerular filtration rate; IgG4-RD, IgG4-related disease; RPF, retroperitoneal fibrosis.
[a]For those with both renal and RPF, reason for inclusion given as per renal criteria.
[b]Other organ involvement aside from above: intestinal = 3, thyroid = 1, pituitary = 1, neuropathy = 1, cardiac = 1.

Radiology

Modalities used for renal and retroperitoneal imaging were as follows: computed tomography (CT) (n = 19; 67.9%); ultrasound (n = 7; 25.0%); positron emission tomography−computed tomography (PET-CT) (n=5; 17.2%); and magnetic resonance imaging (MRI) (n = 5; 17.9%). Para-aortic or peri-ureteric RPF was evident in 14 patients (50%). This was associated with ureteric obstruction in 6 patients (21.4%) (bilateral in 1, unilateral in 5). Eleven patients (61.1%) with IgG4-RKD had abnormalities on imaging; multiple low-density lesions were found in 8 patients (44.4%) patients and diffusely enlarged kidneys in 4 patients (22.2%) (1 patient had both features) (Figure 2 for representative images).

Histopathology

In all, 15 patients with IgG4-RKD underwent renal biopsy (Table 3; Figure 3 for representative images); 14 patients (93.3%) had tubulointerstitial nephritis, which was associated with glomerular disease in 3 cases (20.0%), and 1 patient (6.7%) had glomerular disease alone, without associated tubulointerstitial inflammation. Membranous nephropathy was the cause of glomerular disease in all cases.

All patients with TIN had a lymphoplasmocytic infiltrate with fibrosis. The fibrosis was described as "storiform" in 1 specimen; the remaining 13 specimens had fibrosis according to the reporting renal pathologist

Table 2. Laboratory parameters at presentation

Parameter	Entire cohort (n = 28)	Intrinsic renal disease (n = 18)	No intrinsic renal disease (n = 10)	*P* value[a]	Data missing
Proteinuria (1+ or greater on dipstick; or protein:creatinine >30 mg/mmol), n (%)[c]	8 (53.3)	8 (57.1)	0 (0.0)	NR	13
eGFR (ml/min per 1.73 m^2)[b], median (IQR)	40.2 (25.8–69.4)	27.9 (22–44)	60.9 (39.6–83.8)	0.01	1
Creatinine, μmol/l, median (IQR)	163 (102–238)	229 (157–275)	110 (86–139)	0.008	1
Urea, mmol/l, mean (SD)	11.2 (6.0)	13.3 (7.1)	8.6 (3.2)	0.09	8
Serum IgG4 elevated, n (%)[c]	21 (87.5)	14 (93.3)	7 (77.8)	0.53	4
Absolute IgG4, g/l, median (IQR)[d]	2.9 (2.1–5.9)	3.0 (2.6–6.7)	2.4 (1.3–5.7)	0.39	5
IgA, g/l, mean (SD)	2.2 (1.1)	2.1 (1.6)	2.4 (0.9)	0.61	4
IgM, g/l, mean (SD)	1.1 (1.1)	1.3 (1.3)	0.8 (0.2)	0.23	4
IgG, g/l, mean (SD)	15.6 (7.9)	16.3 (8.6)	14.5 (7.5)	0.59	3
Low C3, n (%)[c]	6 (42.8)	5 (41.7)	1 (50.0)	NR	14
Low C4, n (%)[c]	5 (35.7)	4 (33.3)	1 (50.0)	NR	14
ANA positive, n (%)[c]	6 (30.0)	5 (35.7)	1 (16.7)	0.61	8
ANCA positive, n (%)[c]	1 (5.8)	1 (8.3)	0 (0.0)	0.99	11
ESR, median (IQR)	28 (16–82)	29 (17–82)	24 (11.5–62.5)	0.50	9
CRP, mean (SD)	40.4 (80.0)	8.8 (10.0)	72 (106)	NR	13

ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; IQR, interquartile range; NR, not recorded.
[a]Comparisons are made only between the groups for parameters with data available in >50% of patients in both groups.
[b]The eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) equation (ethnicity unadjusted).
[c]Percentages are given out of the number of patients who had data collected for that parameter.
[d]Due to a change in assay used to measure serum IgG4 at 1 site, 2 baseline IgG4 levels have normal range of 0.04 to 0.86 g/l; all other samples have normal range of 0.1 to 1.3 g/l.

but were not all re-reviewed for a specific pattern of fibrosis by the IgG4-RD multidisciplinary team. One patient with IgG4-RPF had obliterative phlebitis; representative histology is shown in Figure 4. In 13 of 14 patients (92.9%) with TIN, IgG4 staining demonstrated >10 IgG4+ plasma cells per high-power field (in the most concentrated area), and all these patients fulfilled the Raissian criteria for IgG4-TIN.[6] One patient (patient 3) had advanced interstitial fibrosis and did not fulfill the IgG4-TIN criteria (IgG4-RD diagnosed in the pancreas). Assessment of tubular basement membrane immune deposits occurred in 4 patients; 3 of these patients (75%) had evidence of immune complex deposition.

Treatment

A total of 25 patients (89.3%) were treated with immunosuppression, whereas 3 patients (10.7%) were managed without immunosuppression. All patients who were on immunosuppressive treatment received tapering prednisolone at a mean starting dose of 40 ± 16 mg/d. One patient was pulsed with 3 doses of i.v. methylprednisolone prior to starting oral prednisolone. Four patients (16.0%) were treated with a steroid-sparing agent as part of initial treatment alongside prednisolone; azathioprine was used in all of these patients. Five patients (35.7%) with IgG4-RPF underwent ureteric stenting, and 1 patient (7.1%) underwent surgical ureterolysis.

Relapse

The mean follow-up duration was 60 ± 48 months. Thirteen patients (46.4%) with IgG4-RKD and IgG4-RPF had a relapse at any site after initial treatment (10 [55.6%] if intrinsic renal disease and 3 [30.0%] if no intrinsic renal disease, $P = 0.25$). Relapse occurred at median of 18 (IQR, 12–36) months after renal/RPF diagnosis. Relapse occurred in 9 patients (56.3%) on no or minimal immunosuppression, and in 4 patients (33.3%) on maintenance immunosuppression ($P = 0.28$). The sites of relapsed disease were the kidney (n = 8, 61.5%), retroperitoneum (n = 2, 15.4%), hepatopancreatobiliary system (n = 2, 15.4%), and peripheral nervous system (peripheral neuropathy) (n = 1, 7.7%).

All patients with relapse were treated with immunosuppression. Twelve patients (92.3%) had steroids restarted or the dose escalated, and 7 patients (53.8%) had a steroid-sparing agent added (mycophenolate mofetil in 3 patients, azathioprine in 3 patients, and rituximab in 1 patient).

Renal and Patient Outcomes

Four patients who had incomplete follow-up data were excluded from the outcome analysis. In patients with complete data (n = 24), improvement was seen in renal function overall with the latest and presenting median eGFR 59 ml/min per 1.73 m^2 (IQR, 37–75) and 40.5 ml/min per 1.73 m^2 (IQR, 26–70), respectively ($P = 0.23$), and median creatinine 114 μmol/l (IQR, 98–165) and 162 μmol/l (IQR, 102–237) ($P = 0.057$). In addition, reductions in serum IgG4 levels were observed; latest serum IgG4 was 1.6 g/l (IQR, 0.6–2.5) compared to 2.8 g/l (IQR, 2.1–5.7) at presentation ($P = 0.026$). In patients with IgG4-RKD, latest eGFR was 53 ml/min per 1.73 m^2 (IQR, 35–65) compared to 27.9 ml/min per 1.73

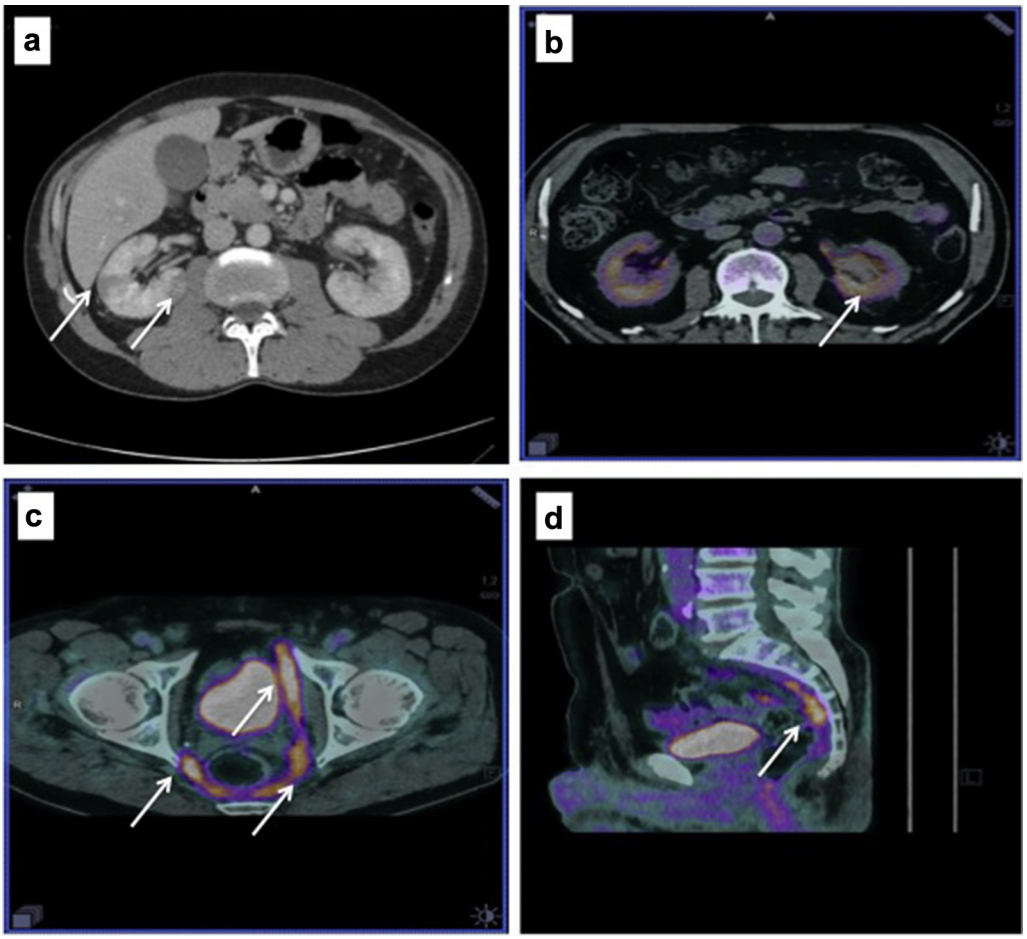

Figure 2. Representative imaging of IgG4-related kidney disease (IgG4-RKD) and IgG4-related retroperitoneal fibrosis (IgG4-RPF). (a) Computed tomography images of multiple low density renal lesions in IgG4-RKD. (b) Positron emission tomography–computed tomography (PET-CT) image of left-sided ureteric obstruction and hydronephrosis in IgG4-RPF. (c) Axial PET-CT image of retroperitoneal fibrosis in IgG4-RPF. (d) Sagittal PET-CT images of presacral retroperitoneal inflammation in IgG4-RPF.

m^2 (IQR, 22–42) at presentation ($P = 0.057$), and latest creatinine 125 μmol/l (101–166) compared to 229 μmol/l (IQR, 160–272) at presentation ($P = 0.048$) (Figure 5).

Renal function was stable or improved in 19 patients (79.2%); 5 patients (20.8%) had progressive deterioration in renal function, including 2 (8.3%) who reached ESRD, 1 of whom underwent renal transplantation. Progressive renal disease occurred in 4 patients (25.0%) with intrinsic renal disease and in 1 patient (11.1%) with RPF ($P = 0.62$). Of those who progressed (patient numbers 4, 13, 15, 18, and 25; Supplementary Table S1), 3 patients progressed off immunosuppression (patient 13 relapsed shortly after stopping steroid, patient 15 was lost to follow-up and represented off immunosuppression with near-ESRD, and patient 25 was treated conservatively, given frailty); 1 patient progressed on low-dose immunosuppression (patient 18, 2 mg/d prednisolone); and 1 patient progressed despite steroid-sparing therapy (patient 4, azathioprine 100 mg/d). Overall, progression occurred in 1 patient (9.1%) on maintenance immunosuppression, and in 4 patients (28.6%) on no or minimal immunosuppression.

In patients with membranous nephropathy (patient numbers 1, 10, 12, and 15), proteinuria in 1 patient (patient 1) completely resolved with conservative management; 1 patient (patient 15; Supplementary Table S1) was lost to follow-up and represented near ESRD, as above; and 1 patient (patient 12) has had persistent nephrosis (>3 g/d proteinuria) despite 3 months of steroid treatment for associated IgG4-TIN. The final patient (patient 10) had evidence of old membranous nephropathy on biopsy, without clinically significant proteinuria at the time of presentation or during follow-up thereafter.

Malignancy and Mortality

One patient with IgG4-RKD or IgG4-RPF developed a malignancy (basal cell carcinoma) after diagnosis. There were no deaths.

The key findings and characteristics of patients with renal and RPF involvement in this study are summarized in Supplementary Tables S2 and S3, respectively,

Table 3. Renal biopsy findings in patients with IgG4-RKD

Patient number	Renal histology overview: TIN, glomerular disease, both	Glomerular light microscopy abnormalities (aside from focal sclerosis)	Glomerular deposits on IF or EM	Tubulointerstitial light microscopy: 1. LPC infiltrate, 2. storiform fibrosis, 3. obliterative phlebitis	IgG4+ plasma cells/hpf	IgG4+/IgG, %	LPC infiltrate patchy or diffuse	TBM deposits on IF or EM	Fulfills Raissian TIN criteria
1	Membranous (no TIN)	Mesangial matrix expansion, thickened capillary walls, spikes on silver stain	IF: subepithelial IgG and C3 (predominantly IgG4), EM: subepithelial deposits	Moderate fibrosis, no significant inflammatory cell infiltrate	N/A	N/A	N/A	No	No
2	TIN	Normal	No	LPC infiltrate and fibrosis	>10	>40%	Diffuse	TBM deposits on IF	Yes
3	TIN	Normal	No	Scanty LPC infiltrate, advanced fibrosis	NR	NR	Patchy	No	No
4	TIN	Normal	No	LPC infiltrate and fibrosis	>10	NR	Diffuse	No	Yes
5	TIN	Normal	No	LPC infiltrate and fibrosis	>10	NR	Diffuse	TBM deposits on IF	Yes
6	TIN	Normal	No	LPC infiltrate and fibrosis	>10	NR	Diffuse	NR	Yes
7	TIN	NR	NR	LPC infiltrate and fibrosis	>10	NR	Diffuse	NR	Yes
8	TIN	Normal	No	Mild LPC infiltrate and fibrosis	>10	NR	NR	NR	Yes
9	TIN	Normal	No	LPC infiltrate and fibrosis	>10	NR	NR	No	Yes
10	TIN, membranous (old)	Normal	EM: small epithelial spaces consistent with resolved deposits in a few capillary loops (suggesting mild membranous at some stage)	LPC infiltrate and fibrosis	>10	>40%	NR	NR	Yes
12	TIN, membranous	Thickening basement membranes with spikes on silver stain	Immunoperoxidase: granular deposition IgG and C9	LPC infiltrate	>10	>40%	Patchy	NR	Yes
13	TIN	Normal	No	LPC infiltrate and fibrosis (mild)	>10	>40%	Patchy	NR	Yes
14	TIN	Shrunken glomeruli	No	LPC infiltrate and fibrosis (marked)	>10	>40%	Patchy	NR	Yes
15	TIN, membranous	Thickening of Bowman capsule and ischemic wrinkling GBM. Spikes on silver stain.	IF: strongly positive IgG4, and C3, in glomerular basement membrane. EM: subepithelial deposits	LPC infiltrate, storiform fibrosis, obliterative phlebitis	>10	NR	Diffuse	Yes	Yes
18	TIN	1 Crescent	No	LPC infiltrate and fibrosis	>10	>40%	NR	NR	Yes

EM, electron microscopy; GBM, glomerular basement membrane; hpf, high-power field; IF, immunofluorescence; IgG4-RKD, IgG4-related kidney disease; LPC, lymphoplasmocytic; N/A, not applicable; NR, not recorded; TBM, tubular basement membrane; TIN, tubulointerstitial nephritis.

and compared to those of previous cohorts of patients with IgG4-RKD[6–8,11] and IgG4-RPF.[9,12–14]

DISCUSSION

We have described the clinicopathological characteristics of IgG4-RKD and IgG4-RPF in a multicenter IgG4-RD cohort from the UK. The prevalence of IgG4-RKD was 11.7%, and the prevalence of IgG4-RPF was 9.1%. Patients were largely elderly men, with multisystem features of IgG4-RD. Renal function was worse at presentation in those with intrinsic renal disease, and complement was low in 50% of those with IgG4-RKD. The predominant histological finding in IgG4-RKD was IgG4-TIN; 27% of patients with renal biopsy had membranous nephropathy. Most patients were treated with steroids initially, with good response, although 46.4% of patients had an IgG4-RD relapse, most often in the kidney. Steroid-sparing agents were used more commonly to treat relapsed disease. Progressive renal impairment occurred in 28.6% of patients on no or minimal immunosuppression, with 2 patients

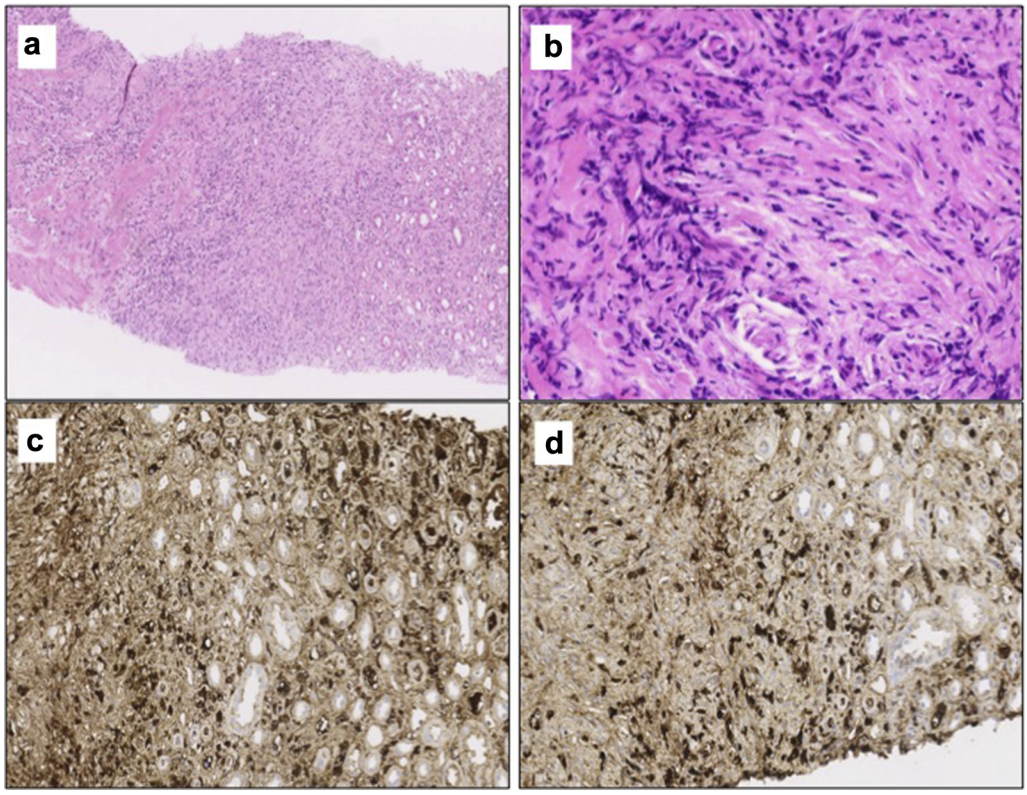

Figure 3. Representative histology of IgG4-related tubulointerstitial nephritis (IgG4-TIN). (a) Hematoxylin and eosin stain demonstrating fibrosis and a dense inflammatory cell infiltrate rich in plasma cells and eosinophils with few small lymphocytes (original magnification ×40). (b) Storiform pattern of fibrosis. (c) IgG stain. (d) IgG4 stain showing >30 IgG4+ plasma cells (high-power field) (original magnification: b-d, ×100).

reaching ESRD, 1 of whom underwent renal transplantation.

Interpretation

Renal and RPF involvement in IgG4-RD has been described in a number of general IgG4-RD cohorts in Asia and the United States.[21–30] Renal and retroperitoneal involvement was demonstrated in a median of 13% (range, 7%–44%) and 19% (range, 2%–32%) of patients across these studies. This compares to renal and RPF involvement of 11.7% and 9.1% in our cohort, respectively. Variation can be attributed to criteria used to define renal and RPF involvement, and the nature of the cohorts included. Regardless of this, renal and retroperitoneal disease represent major organ manifestations of IgG4-RD.

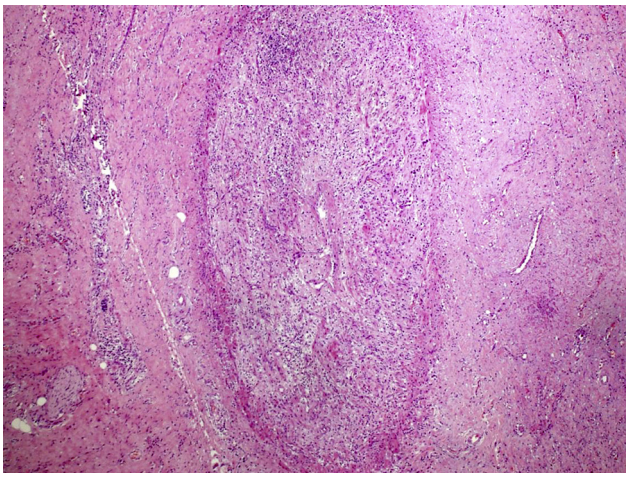

Figure 4. Hematoxylin and eosin stain demonstrating obliterative phlebitis in a patient with IgG4-related retroperitoneal fibrosis (IgG4-RPF) (original magnification ×200).

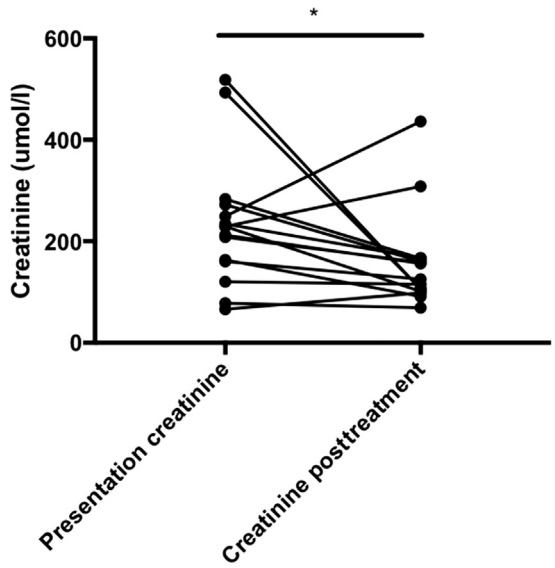

Figure 5. Serum creatinine at baseline and posttreatment (at latest review) in patients with IgG4-related kidney disease (IgG4-RKD) (patient who underwent transplantation excluded).

Presentation of IgG4-RKD and IgG4-RPF is varied, as exemplified by the vignettes (Supplementary Table S1) of each case in this cohort. Symptoms may be related to renal and RPF involvement themselves (e.g., nephrosis in membranous nephropathy, back pain and leg swelling due to impaired venous return in RPF), may be related to other organ disease (most commonly abdominal pain and jaundice with pancreatic/hepatobiliary disease in our cohort), or the disease may present with an unexplained systemic illness (although features of marked inflammation such as fever and night sweats are rare). IgG4-RKD and IgG4-RPF may become apparent during investigation of unexplained renal impairment, may be an incidental finding on imaging, or may be an unexpected histological finding, often in cases of presumed cancer. Most patients have multisystem disease; in this cohort and others, renal disease rarely occurred alone.[24]

Renal function in patients with IgG4-RKD was moderately impaired at presentation, (median creatinine 229 μmol/l), within the range reported in other cohorts[6–8] (147–318 μmol/l). Renal impairment is less common in IgG4-RPF unless there is ureteric obstruction, particularly bilateral. Mild-to-moderate hemoproteinuria occurred in just over half of the patients with IgG4-RKD; this was understandably more severe in patients with glomerular disease.

Consistent with other cohorts of IgG4-RKD, most patients had elevated serum IgG4 (not a universal finding in IgG4-RD generally), and 50% had low complement C3 or C4. IgG4 levels may not be elevated in nephrotic syndrome, due to urinary loss of all Igs; in this situation, we assess the ratio of serum IgG4 to total IgG. Hypocomplementemia is more common in IgG4-RKD than in other manifestations of IgG4-RD, and is somewhat unexplained. The IgG4 subtype has limited ability to fix complement through the classical pathway, and complement consumption may be the result of increased activity of other Ig subtypes, IgG1 and IgG3, or through IgG4 complement activation via the lectin pathway. Hypocomplementemia and TIN (with or without glomerular disease) has been described, albeit rarely, in primary Sjögren's syndrome (complement is maintained in most primary Sjögren's syndrome—TIN patients), and such patients may also have lacrimal and salivary gland disease.[31,32] Although antinuclear antibody is detectable in IgG4-RKD (35% patients in this study), extractable nuclear antigens are rare, whereas anti-SSA/Ro and anti-SSB/La antigens are normally detectable in primary Sjögren's syndrome—TIN.

Abnormalities on renal imaging were found in 61% of patients with IgG4-RKD in this cohort: multiple low-density lesions in 44%, and diffusely enlarged kidneys in 22%. These findings have been found in 40% to 46.5% and 4.9% to 30.4%, respectively, in previously published IgG4-RKD cohorts.[6–8] Thickening of the renal pelvis is another reported finding in IgG4-RD, but this was not seen in any patients in this study. CT was the most common mode of renal imaging, including PET-CT, which is increasingly used. Radiation exposure, however, must be considered when using these techniques, particularly given the association of IgG4-RD and malignancy.[16]

Lymphoplasmocytic infiltration, with predominantly IgG4+ plasma cells (i.e. IgG4-TIN) with associated fibrosis, was the most common renal biopsy finding in our cohort, consistent with other series. Plasma cells are polyclonal or oligoclonal, distinguishing it from lymphomatous infiltration of the kidney, and granulomatous inflammation is not reported (this feature points more toward other causes of TIN, including sarcoid, tuberculosis, or a granulomatous form of drug-induced TIN).[33] Unlike fibrosis in other organs, the characteristic storiform pattern was seen less commonly in the kidney, and similarly obliterative phlebitis, a feature of IgG4-RD at other sites, was rare. Tubular immune deposits may occur in up to 83% of patients with IgG4-TIN.[6] Tubular immunostaining or electron microscopy was performed and reported in only a minority of our historical biopsy results; tubular deposits were present in 75% of cases when it occurred.

TIN may be accompanied by glomerular disease, in 9% to 39% of cases from previous reports, and in 27% of biopsy results in our series. All glomerular disease in this study was membranous nephropathy, the most common glomerular disease associated with IgG4-RD,[34] but other patterns have been reported including IgA nephropathy and mesangioproliferative and membranoproliferative glomerulonephritis.[6,10] Unlike the majority of patients with primary membranous nephropathy, patients with IgG4-RD do not have detectable antibodies to the phospholipase A2 receptor (PLA2R)[35]; antibodies to other podocyte antigens, such as carbonic anhydrase II, have been described.[36] Notably, as occurred in 1 patient in our series, membranous nephropathy may occur without associated TIN, and therefore a diagnosis of IgG4-RD should be considered in patients with membranous nephropathy without other obvious cause, particularly if anti-PLA2R negative.

There are no randomized controlled studies to guide the management of IgG4-RD. Lymphoplasmocytic infiltration (including IgG4-TIN and IgG4-RPF) is usually quickly responsive to steroid, and the majority of patients in this and other cohorts were treated with

oral prednisolone (mean starting dose 40 mg/d in this study) first line. Whether to use a steroid-sparing agent as part of therapy is less clear. Renal function improved in most patients, but, as demonstrated by cases in this and other studies, IgG4-RD is often a relapsing disease (46.4% of our patients relapsed, most often in the kidney), which may lead to progressive and permanent organ damage (11.1% with IgG4-RKD reached ESRD). Steroid therapy has a plethora of unwanted side effects (e.g., worsening diabetes including insulin dependence, and osteoporotic crush fractures in our cohort), and the use of a steroid-sparing agent permits longer-term immunosuppression, while avoiding these.[37] Steroid-sparing agents were used in 16% of patients as part of initial therapy and in 54% patients with relapsed disease in this study; an antiproliferative (azathioprine or mycophenolate mofetil) or rituximab was used. Combined therapy with rituximab and cyclophosphamide has recently been reported in IgG4-RKD with good outcomes in a small number of patients.[38] Future management will depend on patient stratification combined with close follow-up to identify those patients more likely to progress toward ESRD, and in whom more intensive therapy may be beneficial. The development of national and international IgG4-RD registries, such as the European Association for the Study of the Liver (EASL) IgG4-RD Registry, is an essential part of enabling this process.[39]

Unlike lymphoplasmocytic inflammation, there are no data to suggest that membranous nephropathy in IgG4-RD is steroid responsive; we approach membranous in IgG4-RD in the same way as we manage primary membranous nephropathy. One patient underwent transplantation in our cohort; IgG4-RD recurrence has recently been reported in a renal allograft,[40] but whether immunosuppression protocols should be modified in patients with IgG4-RD undergoing transplantation is unknown.

Strengths and Limitations

This study is the first to report the clinical, radiological, and pathological features of renal and retroperitoneal involvement in a UK cohort of IgG4-RD patients. It included patients from multiple centers, with follow-up data in most. We have compared our findings to other major cohorts of IgG4-RKD and IgG4-RPF patients, largely reported from North America and Asia. The London–Oxford IgG4-RD cohort was established by gastroenterologists, and therefore pancreatohepatobiliary disease may be overrepresented and renal or urological disease underrepresented. The retrospective nature of the study means that data may be affected by recall bias, and some data are missing. This includes ethnicity, and details of IgG4 and complement levels before and after initiation of therapy, particularly in patients with IgG4-RPF, and therefore comparisons in these and other parameters between IgG4-RKD and IgG4-RPF patients were difficult to make. Precise details of IgG4 staining (e.g., number of IgG4+ cells) and the pattern of fibrosis (i.e., storiform or not) were not always reported, and not all renal biopsy specimens could be re-reviewed or re-stained. Similarly, details of immunofluorescence and electron microscopy, particularly tubular, were available only in a minority of patients.

In conclusion, IgG4-RKD and IgG4-RPF represent major organ manifestations of IgG4-RD, and the characteristics of patients within the UK are similar to those of patients in other parts of the world. The predominant renal manifestations are IgG4-TIN and IgG4-related membranous nephropathy. Although most patients responded to immunosuppressive therapy, IgG4-RKD frequently relapsed, and the role of steroid-sparing agents as part of initial maintenance therapy needs to be established. End-stage renal disease may occur, in particular with delayed presentation or without treatment. Transplantation may be undertaken in IgG4-RD patients, but long-term outcomes in these patients are yet to be determined.

DISCLOSURE

All the authors declared no competing interests.

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STUDY REGISTRATION

The study is registered on the UK National Institute for Health Research (NIHR) portfolio as study number 10776.

AUTHOR CONTRIBUTIONS

RE, GW, EB, and EC designed the study. RE, TC, GC, BO, RP, MJ, and EC acquired the data. RE, TC, TC, GC,

and EC analysed the data. RE, ADS, JC, RP, GW, EB, and EC interpreted the data. RE, GW, EB, and EC drafted the manuscript. ADS, RP, JC, MJ, BO, EB, GW revised the manuscript. All authors have approved the final version and agree to be accountable for all aspects of the work.

SUPPLEMENTARY MATERIAL

Table S1. Structured vignettes documenting history of patients with IgG4-RKD and IgG4-RPF.

Table S2. Previous cohorts of IgG4-RKD.

Table S3. Previous cohorts of IgG4-RPF.

Supplementary material is linked to the online version of the paper at www.kireports.org.

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