Validation of the 2019 ACR/EULAR criteria for IgG4-related disease in a Japanese kidney disease cohort: a multicentre retrospective study by the IgG4-related kidney disease working group of the Japanese Society of Nephrology

IgG4-related disease (IgG4-RD) is a fibroinflammatory condition that can affect various organs. The kidney is one of the organs most frequently affected and IgG4-related tubulointerstitial nephritis (TIN) is the most dominant feature.[1] However, several radiologically characteristic lesions within the kidney have also been shown to be diagnostic for IgG4-RD affecting the kidney, in the setting of definitively diagnosed IgG4-related lesions in extrarenal organs.[2] Therefore the term 'IgG4-related kidney disease (IgG4-RKD)' has been proposed as a comprehensive term for the renal lesions associated with IgG4-RD.[2 3]

In 2011, the IgG4-RKD working group of the Japanese Society of Nephrology proposed diagnostic criteria for IgG4-RKD.[4] Recently, we validated those criteria in a Japanese kidney cohort and developed a revised version.[5] On the other hand, the 2019 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for IgG4-RD (the ACR/EULAR criteria) were proposed in 2019.[6] According to the latter criteria, exclusion criteria should be applied first to any potential IgG4-RD case. Then, inclusion criteria consisting of eight weighted domains are applied to any case that does not satisfy any of the exclusion criteria, and if the total inclusion points score is ≥20, the case can be classified as 'IgG4-RD'. We validated the ACR/EULAR criteria in the Japanese kidney cohort used in our validation study for IgG4-RKD 2011.[5] Briefly, the cohort comprised Japanese patients diagnosed as having renal injury on the basis of urinalysis, radiographic findings and/or function tests between April 2012 and May 2019, in whom serum IgG4 values and/or data for immunohistological staining of IgG4 in renal biopsy samples were known and for whom sufficient clinical information was available. These patients were classified as IgG4-RD or mimickers based on the ACR/EULAR criteria, and the results were evaluated by expert opinion.

Among the 105 patients included, the expert panel diagnosed 55 as true IgG4-RKD and 50 as mimickers. One patient in each group was used for validation of the ACR/EULAR criteria. The clinical and renal pathological features of each group are shown in table 1. In the IgG4-RKD group, renal biopsy was performed in 51 patients and IgG4-TIN was evident in 48 of them (tissue samples being inadequate in 3). Of the 48 patients with biopsy-proven IgG4-RKD, 34 had extrarenal lesions. Among 14 patients who had only renal lesions, 13 had at least one of the following items: storiform fibrosis demonstrated by renal biopsy, hypocomplementaemia or bilateral renal cortex low-density areas demonstrated by radiology. In seven patients for whom renal histology confirmation was not possible (unavailable in four and inadequate in three), diagnosis of IgG4-RKD was based on radiologically evident bilateral renal cortex low-density areas, in the setting of biopsy-proven IgG4-related extrarenal lesions (n=6) or a definite diagnosis of autoimmune pancreatitis (n=1).

Table 1 Data are available on reasonable request

	IgG4-RKD (n=55)	Mimicker (n=50)	P value
Age at diagnosis of the kidney disease, mean±SD (years)	69.9±9.4	56.7±17.4	<0.001
Male (%)	76.4	44	0.001
Allergy (%)	27.5	36.7	0.393
Serum IgG4 (mg/dL), mean±SD	1028±796	226±261	<0.001
Elevated serum IgG4 (≥135 mg/dL), n/total (%)	54/55 (98.2)	18/50 (36.0)	<0.001
Hypocomplementaemia, n/total (%)	39/55 (70.1%)	7/42 (16.7%)	<0.001
Renal pelvis thickening/soft tissue, n/total (%)	5/55 (9%)	1/50 (2%)	0.20
Bilateral renal cortex low-density areas, n/total (%)	29/55 (52.7%)	7/50 (14.0%)	<0.001
Extrarenal organ(s) involvement, n/total (%)	41/55 (74.5)	20/50 (40.0)	<0.001
Renal biopsy, performed, n/total (%)	51/55 (92.7)	50/50 (100)	0.120
Dense IgG4+PC, n/total (%)	48/51 (94.1)	13/40 (32.5) (not evaluated in 10)	<0.001
Storiform fibrosis in the renal pathology, n/total (%)	28/51 (54.9)	3/50 (6)	<0.001
Renal pathological diagnosis (n)			
	IgG4-TIN (48) with MN (4) with FSGS (1) with mesPGN (2) Inadequate tissue (3)	AAV (8) MPA (5), EGPA (3) Idiopathic TIN (5) Drug-induced TIN (5) Nephrosclerosis (4) Sjögren's syndrome (4) Sarcoidosis (3) MCD (3) Necrotising GN without ANCA (3) MN (3) Others* (12)	

Dense IgG4+PC: dense lymphoplasmacytic infiltration with infiltrating IgG4-positive plasma cells >10/high power field and/or ratio of IgG4-positive plasma cells >40% in the renal pathology.
Others*: TIN and uveitis syndrome (n=2), TIN associated with inflammatory bowel disease (n=2), TIN with IgM-positive plasma cells (n=2), TIN associated with infection (n=2), IgA nephropathy (n=1), diabetic nephropathy (n=1), malignant lymphoma (n=1) and antibody-mediated rejection after renal transplantation (n=1).
AAV, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis; EPGA, eosinophilic granulomatosis with polyangiitis; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; IgG4-TIN, IgG4-related tubulointerstitial nephritis; MCD, multicentric Castleman's disease; mesPGN, mesangial proliferative glomerulonephritis; MN, membranous nephropathy; MPA, microscopic polyangiitis; TIN, tubulointerstitial nephritis.

Four of the 55 IgG4-RKD patients and 24 of the 50 mimickers had exclusion criteria. Of the remaining cases, 50 of 51 IgG4-RKD patients and 1 of 26 mimickers had an inclusion criterion score of ≥20 points (figure 1 and online supplemental table 1). One IgG4-RKD patient, whose autoimmune pancreatitis was the focal swelling type, was misclassified as non-IgG4-RKD. As a result, 50 of the 55 IgG4-RKD patients were classified as IgG4-RKD and 49 of the 50 mimickers were classified as non-IgG4-RKD (sensitivity 90.9%, specificity 98.0%, positive predictive value 98.0% and negative predictive value 90.7%).

Many IgG4-RKD patients had extrarenal lesions and IgG4-positive cell-rich TIN associated with other diseases was effectively excluded on the basis of exclusion criteria. In conclusion, the ACR/EULAR criteria showed an excellent test performance for IgG4-RKD in Japanese patients, although further validation studies of other racial groups will be necessary.

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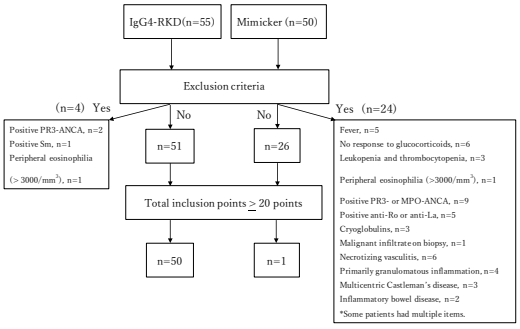

Figure 1 Performance of the American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-related disease in a Japanese kidney cohort. ANCA, antineutrophil cytoplasmic antibody; IgG4-RKD, IgG4-related kidney disease; MPO, myeloperoxidase; PR-3, proteinase 3.

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