

Diagnosis of IgG4-Related Tubulointerstitial Nephritis

Yassaman Raissian,* Samih H. Nasr,* Christopher P. Larsen,[†] Robert B. Colvin,[‡] Thomas C. Smyrk,* Naoki Takahashi,[§] Ami Bhalodia,^{||} Aliyah R. Sohani,[‡] Lizhi Zhang,* Suresh Chari,^{||} Sanjeev Sethi,* Mary E. Fidler,* and Lynn D. Cornell*

*Division of Anatomic Pathology, Department of Laboratory Medicine and Pathology, [§]Department of Radiology, and ^{||}Division of Gastroenterology and Hepatology, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota; [†]Nephropathology Associates, Little Rock, Arkansas; [‡]Pathology Service, Massachusetts General Hospital, Boston, Massachusetts; and ^{||}Department of Pathology, Louisiana State University Health Sciences Center, Shreveport, Louisiana

ABSTRACT

IgG4-related systemic disease is an autoimmune disease that was first recognized in the pancreas but also affects other organs. This disease may manifest as tubulointerstitial nephritis (IgG4-TIN), but its clinicopathologic features in the kidney are not well described. Of the 35 patients with IgG4-TIN whose renal tissue specimens we examined, 27 (77%) had acute or progressive chronic renal failure, 29 (83%) had involvement of other organ systems, and 18 of 23 (78%) had radiographic abnormalities. Elevated total IgG or IgG4 serum levels were present in 79%. All pathologic specimens featured plasma cell-rich TIN, with most showing diffuse, expansile interstitial fibrosis. Immune complexes along the tubular basement membranes were present in 25 of 30 (83%). All specimens had a moderate to marked increase in IgG4+ plasma cells by immunohistochemistry. We used a control group of 175 pathologic specimens with plasma cell-rich interstitial infiltrates that can mimic IgG4-TIN to examine the diagnostic utility of IgG4 immunostaining. Excluding pauci-immune necrotizing and crescentic glomerulonephritis, IgG4 immunohistochemistry had a sensitivity of 100% (95% CI 90–100%) and a specificity of 92% (95% CI 86–95%) for IgG4-TIN. Of the 19 patients with renal failure for whom treatment and follow-up data were available, 17 (89%) responded to prednisone. In summary, because no single test definitively diagnoses IgG4-related systemic disease, we rely on a combination of histologic, immunophenotypic, clinical, radiographic, and laboratory features. When the disease manifests in the kidney, our data support diagnostic criteria that can distinguish IgG4-TIN from other types of TIN.

J Am Soc Nephrol 22: 1343–1352, 2011. doi: 10.1681/ASN.2011010062

IgG4-related systemic disease (IgG4-RSD) has been recognized in the past several years as a systemic autoimmune disease, first recognized in the pancreas as sclerosing or autoimmune pancreatitis (AIP).^{1,2} Now, some form of IgG4-RSD disease has been described in nearly every organ system, including the kidney, liver, gallbladder, other gastrointestinal sites, salivary and lacrimal glands, lung, orbit, breast, retroperitoneum, aorta, lymph nodes, skin, pituitary gland, and prostate.^{1–7} The first description of AIP is attributed to Sarles *et al.*, who speculated on an autoimmune cause due to the presence of significant hypergammaglobulinemia in some patients and absence of evidence of infec-

tion.⁸ Hamano *et al.* recognized the connection of elevated serum IgG4 to AIP⁹ and documented the presence of IgG4-positive plasma cells in affected patients, both in the pancreas and at extrapancreatic sites.¹⁰ Others have delineated the systemic nature of this condition.^{1,7,11}

Received January 17, 2011. Accepted March 10, 2011.

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Lynn D. Cornell, Mayo Clinic, 200 1st Street SW, Rochester, MN 55905. Phone: 507-284-9320; Fax: 507-538-8321; E-mail cornell.lynn@mayo.edu

Copyright © 2011 by the American Society of Nephrology

Renal disease has been associated with IgG4-RSD, usually in the form of plasma cell-rich tubulointerstitial nephritis (TIN).^{12–14} IgG4-TIN can be mass forming, similar to IgG4-related inflammatory lesions in other organs.¹² Indeed, 30% of patients with AIP show evidence of renal parenchymal involvement by TIN based on the distinctive radiographic appearance.¹⁵ Other renal manifestations of IgG4-RSD include membranous glomerulonephritis (MGN) and hydronephrosis associated with IgG4-related retroperitoneal fibrosis.^{10,14}

Groups at Mayo Clinic and in Japan and Korea have proposed diagnostic criteria for IgG4-RSD when it affects the pancreas as AIP.^{16,17} The diagnosis of AIP is based on a combination of serologic (increased IgG and/or IgG4 levels), radiographic (*e.g.*, diffusely enlarged pancreas and pancreatic masses), and histopathologic findings (periductal lymphoplasmacytic infiltrate, storiform fibrosis, and increased IgG4+ plasma cells), presence of other organ involvement, and a positive response to steroid therapy. Diagnostic criteria have not been proposed for distinguishing IgG4-related TIN from other types of TIN. In this study of 35 patients with IgG4-TIN, we examined the histopathologic, immunophenotypic, and ultrastructural features, radiographic and serologic findings, and clinical outcomes, including response to therapy. We compared our findings to the immunophenotypic characteristics of a control group of 175 patients with plasma cell-rich interstitial infiltrates due to causes other than IgG4-RSD. Using these data, we propose diagnostic criteria for IgG4-TIN.

RESULTS

Clinical Features of IgG4-TIN

The average age of the 35 patients was 65 years (range, 20 to 81); 30 (86%) were men. Twenty-seven of 35 patients (77%) had acute or progressive chronic renal failure at the time of renal biopsy. The mean serum creatinine (SCr) in all patients with measurements (*n* = 33) was 3.6 mg/dl (range, 0.9 to 9). Two biopsies were done for nephrotic-range proteinuria; these biopsies showed MGN in addition to TIN, and these patients did not have distinct renal mass lesions radiographically. Three patients underwent nephrectomy or partial nephrectomy. Nine patients (26%) had renal mass lesion(s) found radiographically as the primary indication for biopsy or nephrectomy; 3 of these patients also had chronic renal failure. The mean SCr in patients with specimens for mass lesions was 1.4 mg/dl, whereas it was 4.2 mg/dl in patients with biopsies for renal failure.

Other Organ Involvement

Twenty-nine of 35 patients (83%) had known current or previous clinical, radiographic, and/or histologic evidence of other organ involvement by a systemic inflammatory disease. Most patients with extrarenal involvement had multiorgan involvement. Table 1 lists the sites affected. Of note, no patient showed only lymphadenopathy, cutaneous vasculitis, thyroiditis, or arthritis.

Radiographic Features of IgG4-TIN

In patients with available radiographic data, 18 of 23 (78%) showed radiographic abnormalities. These abnormalities consisted of small low-attenuation lesions, usually bilateral and multiple, or a mass in 14 patients or bilateral markedly enlarged kidneys (≥ 14.5 cm) in 4 patients. (See Table 1.)

Laboratory Features of IgG4-TIN

Overall, 22 of 25 patients (88%) had increased serum total IgG or IgG4 levels or hypergammaglobulinemia. Fifteen of 19 patients (79%) with measurements available had elevated serum total IgG and/or IgG4 levels, with 11 of 15 (73%) with known elevated IgG levels and 11 of 12 (92%) with known elevated IgG4 levels. Six of 18 patients (33%) had peripheral blood eosinophilia. Fourteen of 25 patients (56%) had hypocomplementemia, with decreased serum C3 (11 of 26, 42%) and/or C4 levels (12 of 26, 46%). Ten of 32 patients (31%) had a positive ANA, all but 1 of which were weakly or transiently positive. No patients had current positive tests for hepatitis B or C infection. Two patients had positive antimyeloperoxidase antibodies, but without evidence of a necrotizing or crescentic glomerulonephritis on biopsy. Eight of 27 patients with urine data had >1 g/d proteinuria (range, 0 to 16 g/d), and 6 patients had hematuria. Two patients (both with MGN) had nephrotic-range proteinuria.

Histologic and Immunophenotypic Features of IgG4-Related TIN

By light microscopy (LM), all pathologic specimens by definition showed a diffuse or multifocal TIN with increased plasma cells, as well as mononuclear cells. All but four specimens showed numerous eosinophils that were sometimes prominent. Focal mild mononuclear cell tubulitis was seen in most cases; plasma cell tubulitis was seen rarely. 30 of 35 cases had an expansile interstitial fibroinflammatory process, whereas 5 of 35 cases showed an acute interstitial nephritis pattern with only minimal interstitial fibrosis ($<10\%$ of cortex) and without an expansile interstitial process (pattern A). The ratio of fibrosis to inflammation showed variability from specimen to specimen; some (24 of 35) had a more densely cellular inflammatory lesion with expansile interstitial fibrosis present (pattern B), whereas others (6 of 35) had collagen-rich, paucicellular fibrosis (pattern C). Some specimens showed variability of degrees of fibrosis and inflammation within each tissue sample. Thirty of 35 specimens (86%) showed moderate to severe interstitial fibrosis and tubular atrophy in the biopsy or within areas of the inflammatory mass on nephrectomy samples. In some areas of tubular atrophy, only fragments of residual TBMs could be seen. Three patients with nephrectomy samples showed normal renal parenchyma outside of the inflammatory mass lesion. Two nephrectomy samples revealed a more fibrotic and less inflammatory region at the center of the mass, with a more inflammatory, less fibrotic pattern at the periphery.

No vascular fibrinoid necrosis was identified in any specimen. Glomeruli appeared normal or showed mild mesangial matrix expansion. Three specimens had immunofluorescence (IF) evidence of glomerular immune complex deposits: one showed granular mesangial IgG, C3, and kappa and lambda light chains (patient 35), and two showed MGN with granular glomerular capillary loop IgG, C3, and kappa and lambda light chains (patients 29 and 30).

All 34 IgG4-TIN specimens with sufficient material for immunohistochemistry (IHC) showed moderate to marked increase in IgG4+ plasma cells. Thirteen of 34 showed a moderate increase in IgG4+ cells and 21 of 34 showed a marked increase.

Overall, 25 of 30 specimens (83%) with immunostaining or electron microscopy (EM) performed showed TBM immune complex deposits by IHC for IgG4, IF (22 of 26, 85%), and/or EM (11 of 16, 69%). By IF, all specimens with deposits showed granular TBM staining for IgG. Those specimens with IgG and staining information for other immunoreactants also showed accompanying kappa and lambda light chains, and often accompanying C3 of lesser staining intensity. Three specimens showed TBM granular staining for C1q, two of which also showed TBM IgM, and one other specimen showed IgM without C1q. The TBM deposits were diffuse in 14 patients and focal in 9 patients with data available. By EM the TBM deposits were amorphous and electron dense. (See Figure 1.) TBM deposits were present in areas with interstitial inflammation by EM, and not present in the normal areas of one nephrectomy examined.

TBM deposits were more commonly found in specimens with patterns B (20 of 21, 95%) and C (5 of 6, 83%) than in those with pattern A (0 of 3, 0%). This difference was statistically significant for pattern A *versus* pattern B ($P = 0.002$) and pattern A *versus* pattern C ($P = 0.048$). There was no significant difference in prevalence of positive ANA, hypocomplementemia, elevated serum IgG or IgG4, or presence of other organ involvement in the patients with TBM deposits *versus* those without.

Control TIN Specimens for IgG4 Staining

Control pathologic specimens were obtained by two methods: (1) by biopsy review of all native renal biopsies during a given year (2007) with significant interstitial inflammation and (2) by diagnosis on specimens outside of the given year that could mimic IgG4-TIN clinically, radiographically, and/or histologically and that showed interstitial inflammation.

Within the given year (2007), 414 renal biopsies were identified with moderate or severe interstitial inflammation according to the pathology report, including 167 patients with associated nondiabetic glomerular disease; within this time period, 4492 native kidney biopsies were examined at our institution. Of the biopsies with interstitial inflammation, 82 of 414 (20%) had increased plasma cells, defined for screening purposes as >5 plasma cells/ $\times 400$ magnification (hpf) in ≥ 3 fields, with etiology as follows: 20 (24%) drug effect, 18 (22%) unknown cause, 15 (18%) associated with pauci-immune necrotizing and crescentic glomerulonephritis (GN), 14 (17%)

associated with other glomerular disease (immune-mediated crescentic GN, focal segmental glomerulosclerosis, and diabetes), 9 (11%) autoimmune disease, 2 (2%) pyelonephritis, 2 (2%) confirmed or possible IgG4-TIN, 1 (1%) antiglomerular basement membrane (GBM) nephritis, and 1 (1%) oxalate nephropathy.

Fourteen of 82 biopsies (17%) from the control interstitial inflammation group showed moderate or marked increase in IgG4+ plasma cells, defined as 11 to 30 cells per hpf (moderate) and >30 cells per hpf (marked). These biopsies with increased IgG4+ plasma cells were pauci-immune GN ($n = 6$ of 15 total biopsies stained), TIN due to drug (2 of 20), autoimmune TIN (2 of 9, including 1 of 2 with lupus glomerulonephritis), chronic pyelonephritis (1 of 2), unknown cause (1 of 18), and possible or confirmed IgG4-TIN (2 of 2). Two of these biopsies showed TBM deposits by IF, one with IgG4-TIN and the other with an autoimmune TIN possibly representing lupus interstitial nephritis. None of the other biopsies with TIN with increased IgG4+ plasma cells showed TBM deposits. Stained biopsies from the control time period with no increase in IgG4+ plasma cells were anti-GBM nephritis (0 of 1) and oxalate nephropathy (0 of 1).

An additional 93 biopsies from outside the given year and chosen by diagnosis were stained for IgG4. Specimens with at least moderately increased IgG4+ plasma cells were as follows: 7 of 26 pauci-immune GN, 0 of 19 TIN in patients with a history of acute or chronic pancreatitis (nonautoimmune), 1 of 14 TIN associated with Sjögren syndrome, 2 of 10 pyelonephritis, 1 of 6 unknown cause, 1 of 8 proliferative lupus nephritis with TBM immune deposits, along with 0 of 5 other autoimmune (including 2 biopsies with hypocomplementemic TIN with TBM deposits) and 0 of 5 drug reaction. One of 6 pauci-immune GN showed a focal marked increase in IgG4+ plasma cells, whereas other controls stained showed only a focal moderate increase.

In total, excluding IgG4-RSD and pauci-immune GN, 11 of 131 TIN biopsies (8.4%) studied showed at least a moderate increase in IgG4+ plasma cells. If pauci-immune GN is excluded, the IgG4 stain has a sensitivity of 100% (confidence interval [CI] 0.90 to 1) and a specificity of 92% (CI 0.86 to 0.95) for TIN as part of IgG4-RSD.

Treatment and Clinical Follow-up of IgG4-TIN

Treatment and follow-up clinical information was available in 27 patients, with a mean follow-up time of 14.5 months (range, 1 to 84 months). (See Table 2.) Twenty-one patients, 19 of whom had renal insufficiency at biopsy, were treated with prednisone; two patients received mycophenolate mofetil in addition to prednisone. Two patients required dialysis. Seventeen of 19 patients with renal insufficiency showed a decrease in SCr with treatment that included steroids. The mean pretreatment (including one patient treated with surgery only) SCr was 3.5 mg/dl (range, 1.1 to 8.5), and posttreatment was 1.7 mg/dl (range, 1.0 to 3.3, excluding one patient with end-stage renal disease). Two patients showed no improvement

Table 1. Clinical, histologic, radiographic, and laboratory features of IgG4-TIN

Pt No.	Age/ Gender	Race/ Ethnicity	Renal Specimen	Indication	Histologic Findings	Pattern ^a	IF/TA	TBM Deposits	IgG4 IHC (cells per hpf)	Other Organ Involvement	Renal Imaging findings	SCr	Serum IgG or IgG4	Hyper-gamma- globulinemia	Eosinophilia	Serum C	ANA/ds DNA	UA
1	20 M	AA	Bx	CRF	TIN	B	Mod	Y/diffuse	>30	None known	Bilat enlarged	3.2–3.8	Inc IgG, IgG4	Y	Y	NL	Neg	Neg
2	60 M	Asian	Bx	CRF	TIN	B	Sev	Y/focal	>30	None known	NA	1.6	ND	Y	Unk	Decr C3	Neg	Neg
3	81 F	W	Bx	CRF and mass	TIN	C	Sev	Y/focal	>30	None known	Mult low-atten lesions	1.9	Inc IgG, IgG4	Y	N	NL	Neg	Neg
4	72 M	Unk	Bx	Mass	TIN	B	Sev	ND	11 to 30	Lung, Ao, Panc	Mass	Unk	Inc IgG4	NA	Unk	Decr C3, C4	NA	NA
5	76 M	W	Bx	Mass	TIN	B	Sev	ND	11 to 30	Ao, LA, skin (vasculitis)	Mass	1.7	ND	Y	N	Decr C3, C4	Neg/low pos	Neg
6	72 M	W	Bx	CRF	TIN	B	Sev	Y/focal	11 to 30	Sclerosing cholangitis	NA	2.5	Inc IgG, IgG4	Y	N	NL	Neg	Prot
7	47 M	AA	Bx	CRF	TIN	B	Sev	Y/diffuse	>30	Sal, LA	Bilat enlarged	3.0	Unk	Y	N	NA	Neg	Neg
8	72 M	W	Bx	CRF	TIN	B	Sev	Y/diffuse	11 to 30	PBC, Panc, thyroid	Mass/mult low-atten lesions	4.2	Inc IgG	NA	Unk	NL	Neg	Neg
9	48 M	W/Hisp	Bx	A on CRF	TIN	C	Sev	Y/diffuse	11 to 30	Pericarditis, inflammatory arthritis	NL	2.0	Inc IgG	NA	N	NL	Neg	Hem/Prot
10	84 M	W	Bx	A on CRF	TIN	B	Sev	Y/diffuse	>30	Panc, lung	NL	5.7	Inc IgG	NA	N	Decr C3, C4	Neg	Pro
11	66 M	W	Neph	Mass	Focal TIN	B	Sev	Y by EM	>30	Panc, LA, Sal, biliary tree	Mass	1.1	NL	NA	N	NA	Neg	Neg
12	62 M	W	Bx	CRF	TIN	C	Sev	Neg	>30	Testicular inflammatory mass, sinusitis	Mult low-atten lesions	3.4	Inc IgG, IgG4	NA	Unk	Decr C4	Neg	NA
13	69 M	W	Bx	CRF	AIN	A	Mild	ND	11 to 30	Panc, lung, liver	NA	3.8	NL	NA	Unk	NA	Neg	Unk
14	74 M	W	Bx	ARF	TIN	B	Sev	Y/diffuse	>30	Panc, lung, liver, GB, skin	NA	6.3	NL	NA	Unk	NA	NA	Pro
15	78 M	W	Bx	CRF	TIN	B	Mod	Y/diffuse	11 to 30	(vasculitis) LA, hepatitis	Cysts	5.4	Inc IgG4	NA	N	NL	Pos	Neg
16	76 M	W	Bx	ARF	AIN	A	Mild	Neg	>30	None known	NA	8.5	Inc IgG4	NA	N	NL	dsDNA Neg	NA
17	52 M	AA	Bx	A on CRF	TIN	B	Sev	Y/focal	>30	Liver, LA, paraspinal soft tissue mass	Bilat enlarged	9.0	Inc IgG, IgG4	NA	Y	Decr C3	Unk	NA
18	55 M	Am Ind	Bx	Masses	AIN	A	Mild	ND	11 to 30	Lac, Pit, RF, lung, thyroid, LA	Mult low-atten lesions	0.9	Inc IgG	Y	N	NL	Pos	Neg
19	59 F	W	Bx	CRF and Mass	TIN	B	Sev	Y/focal	11 to 30	Panc	Mult low-atten lesions	2.6	Inc IgG4	Neg	Y	NA	Neg	Neg
20	63 M	W	Neph	Mass	Focal TIN	B	Sev	ND	11 to 30	Panc, RF, LA, ureter	Mass	1.4	NL	NA	N	NA	NA	NA
21	60 F	W	Bx	CRF	TIN	B	Sev	Y	>30	Arthritis, LA	Bilat enlarged	2.8	ND	Y	N	Decr C3, C4	Pos	Pro
22	60 M	W	Bx	CRF	TIN	B	Sev	Y/diffuse	>30	Sinusitis	NA	3.3	Unk	NA	Unk	NL	Neg	Tr Hem/ Prot

Table 1. Continued

Pt No.	Age/ Gender	Race/ Ethnicity	Renal Specimen	Indication	Histologic Findings	Pattern ^a	IF/TA	TBM Deposits	IgG4 IHC (cells per hpf)	Other Organ Involvement	Renal Imaging findings	SCR ^c	Serum IgG or IgG4	Hyper-gamma- globulinemia	Eosinophilia	Serum C	ANA/ds DNA	UA
23	77 M	W	Bx	CRF	TIN	B	Sev	Y/diffuse	>30	None known	NA	4.4	Unk	Y	Unk	Decr C3, C4	Neg	Hem/Prot
24	66 M	W/Hisp	Bx	ARF	TIN	B	Sev	Y/diffuse	>30	Sal	NA	5.7	Unk	NA	Unk	Decr C3, C4	Pos/Neg	Hem/Prot
25	64 M	W	Bx	A on CRF	TIN	B	Sev	Y/diffuse	11 to 30	None known	NA	4.3	Unk	NA	Y	Decr C3, C4	Neg	Unk
26	57 M	W	Bx	ARF	TIN	C	Sev	Y/diffuse	11 to 30	Panc	NA	Inc	Unk	NA	Unk	NA	NA	Unk
27	72 M	W	Bx	ARF	TIN	B	Sev	Y/focal	11 to 30	Panc, lung	NA	3.2	Unk	NA	Unk	Decr C3, C4	Pos/Neg	Hem/Prot
28	71 M	W	Bx	ARF	TIN	C	Sev	Y/diffuse	>30	Panc	NA	2.8	Unk	Y	N	Decr C3, C4	Pos/Neg	Tr Prot
29	67 F	W	Bx	CRF, proteinuria	MGN, focal TIN	B	Mod	Neg	>30	Sal	NL	1.2	Inc IgG4	Y	Y	NL	Neg	Prot (4g/d)
30	75 M	Unk	Bx	A on CRF, proteinuria	MGN, AIN	A	Mild	Neg	>30	None known	Bilat enlarged	6.6	Unk	NA	N	NL	Neg	Prot (16g/d)
31	71 M	W	Bx	Mass	TIN	B	Sev	Y/focal	>30	Panc, lung, sal	Mult low-atten lesions	0.9–1.1	Inc IgG, IgG4	NA	Unk	NA	Neg	Neg
32	57 M	W	Neph	Mass	Focal TIN	A	Mild	Neg	>30	Panc, sal	Mass	NL	Unk	NA	Unk	NA	NA	Neg
33	68 F	W	Bx	Mass	TIN	B	Sev	Y/diffuse	>30	Panc, liver, orbital pseudotumor, colon (IBD)	Mult low- atten lesions	0.9–1.1	Inc IgG	NA	Unk	Decr C4	Pos	Neg
34	78 M	W	Bx	CRF	TIN	C	Sev	Y/focal	NA ^b	Panc, liver	NL	3.0	Inc IgG	NA	Unk	Decr C3, C4	Pos	Unk
35	45 M	Unk	Bx	CRF and mass	TIN	B	Sev	Y/focal	>30	Liver, lung	Mult low-atten lesions	7.0	Unk	NA	Y	NA	Neg	Neg

AA, African-American/non-Hispanic; AIN, acute interstitial nephritis; Am Ind, American Indian/Alaskan Native; Ao, aortitis; Atten, attenuation; Bilat, bilateral; Bx, biopsy; C, complement; Dec, decreased; GB, gallbladder; Hem, hematuria; Inc, increased; IBD, inflammatory bowel disease; IF/TA, interstitial fibrosis/tubular atrophy; Lac, lacrimal gland (dacryoadenitis); Mult, multiple; N, no; ND, not done; Neph, nephrectomy; NL, normal; Panc, pancreas (AIP); PBC, primary biliary cirrhosis; Prot, proteinuria; RF, retroperitoneal fibrosis; Sal, salivary gland (sialadenitis); Sev, severe; Tr, trace; UA, urinalysis; Unk, unknown; W, white/non-Hispanic; W/His, white/Hispanic; Y, yes.

^aBased on predominant pattern in tissue sample.

^bInsufficient material for staining.

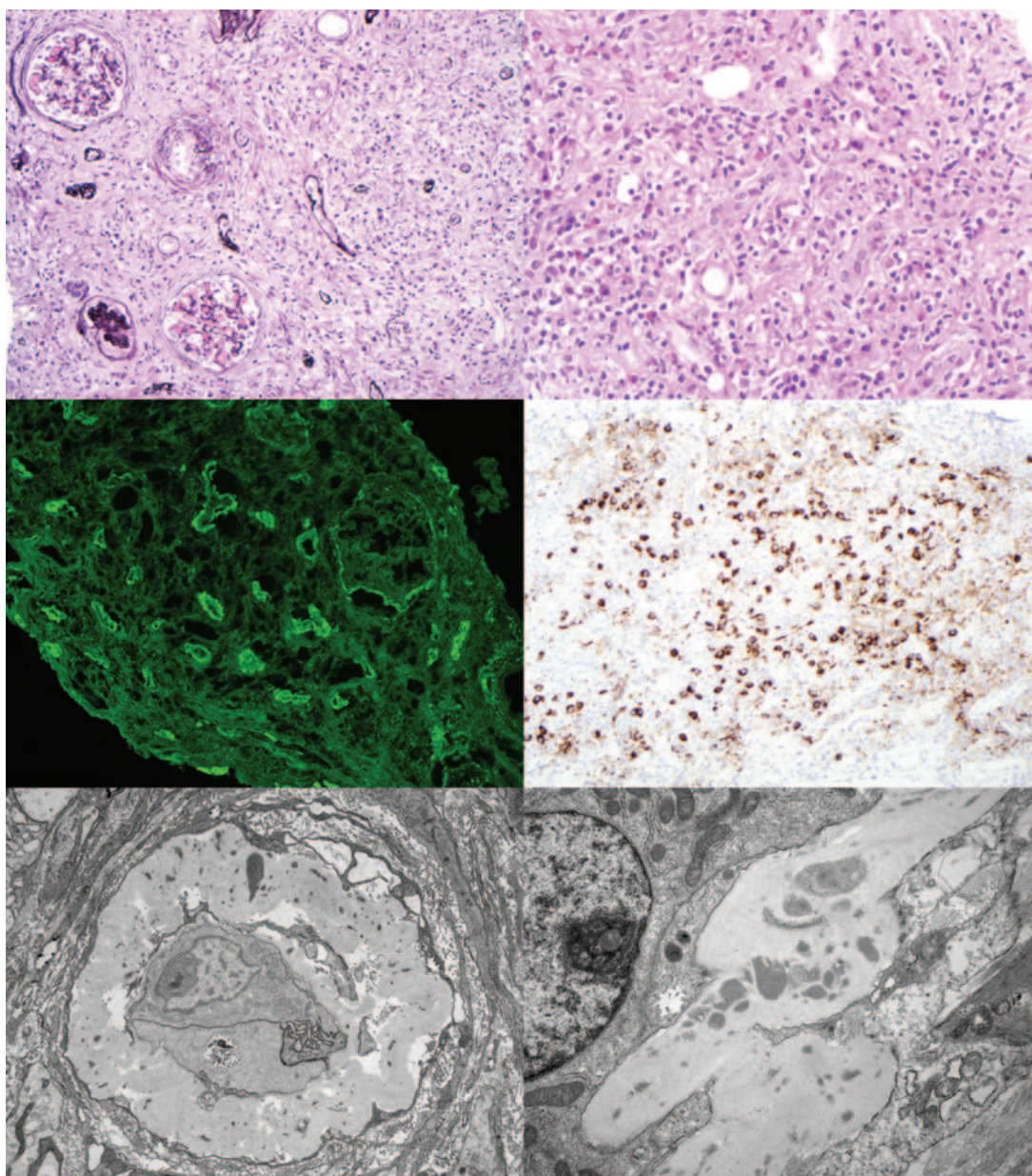


Figure 1. Typical pathologic features of IgG4-related TIN. Representative light, immunofluorescence, and electron microscopy images from patient #8. Top, left: An expansive, destructive fibroinflammatory process with residual tubular basement membranes seen on a silver stain. Glomeruli are unaffected except for periglomerular fibrosis and global glomerulosclerosis (Jones-methenamine silver, $\times 200$). Top right: The interstitial infiltrate is composed of mononuclear cells, plasma cells, and several eosinophils. Mononuclear cell tubulitis is seen focally (hematoxylin and eosin, $\times 400$). Middle left: Immunofluorescence for IgG shows diffuse granular tubular basement membrane staining, as well as Bowman's capsule staining. The glomerular tuft is negative (immunofluorescence IgG-FITC, $\times 200$). Middle right: Immunohistochemical staining for IgG4 shows a marked increase in IgG4-positive plasma cells in the infiltrate ($\times 200$). Bottom left: Electron microscopy reveals thickened tubular basement membranes with scattered electron dense immune complex deposits in an atrophic tubule ($\times 5800$). Bottom right: Amorphous tubular basement membrane deposits ($\times 9700$).

with steroids at 1- and 6-month follow-up: one patient remained on dialysis and developed end-stage renal disease despite steroid treatment, and another patient died with chronic renal failure 11 months after the biopsy. Two patients showed a response to steroid therapy but experienced a relapse with increased SCr upon steroid taper. Two patients with normal

renal function were also treated with prednisone and showed continued normal SCr at 1.1 and 1 mg/dl on follow-up. One patient (patient 20) was treated with nephrectomy only and showed decreased SCr on follow-up from 1.4 to 1.0 mg/dl at 84-months postnephrectomy. Five patients were not treated medically or surgically and showed increased or continued el-

Table 2. Treatment and follow-up of IgG4-TIN

Pt No.	Treatment	SCr at Bx	f/u SCr	Response	Length of f/u (months)
1	Pred	3.2 to 3.8	2.2	Yes; initial response and then relapse with steroid withdrawal	10
2	None	1.6	1.6	NA; stable incr SCr	9
3	Pred	1.9	1.6	Yes	5
5	None	1.7	1.6	NA; stable incr SCr	1
6	Pred	2.5	2.8	No	6
7	Pred	3.0	1.5	Yes	12
8	Pred	4.2	1.5	Yes	6
9	Pred	2.0	1.5	Yes	3.5
10	Pred/MMF/dialysis	5.7	2.9	Yes	5
11	Pred/MMF	1.1	1	Stable normal SCr	6
12	Pred	3.4	2.1	Yes	19
13	Pred	3.8	1.4	Yes	3
14	Pred	6.3	1.2	Yes	2
15	Pred/dialysis	5.4	ESRD	No	1
16	Pred	8.5	2.3	Yes	3
18	Pred	0.9	1.1	Stable Scr	14
19	Pred/MMF	2.6	1	Yes	36
20	Surgery only	1.4	1	Yes	84
21	Pred	2.8	1.3	Yes	13
22	Pred	3.3	1.5	Yes	4
23	None	4.4	4.4	NA; stable incr SCr	17
24	Pred	5.7	3.3	Yes	6
27	Pred	3.2	1.5	Yes	1
30	Pred	6.6	2.5	Yes	1.1
31	None	0.9 to 1.1	1.8	NA; incr SCr	20
33	None	0.9 to 1.1	1.2 to 1.8	NA; incr SCr	64
34	Pred	3.0	1.0 to 2.9	Yes; initial response and then relapse with steroid withdrawal	40

f/u, follow-up; Pred, prednisone; MMF, mycophenolate mofetil; Bx, biopsy; SCr, serum creatinine; Incr, increased.

evated SCr (average 2.2 mg/dl, range 1.2 to 4.4) from 1 to 64 months after diagnosis (average 26 months). There was no correlation between histologic pattern and response to therapy, and even patients with extensive fibrosis on biopsy showed response to steroid treatment.

DISCUSSION

TIN is a disease pattern with heterogeneous causes, both immune and nonimmune. The clinical presentation, laboratory results, and biopsy features are all considered to make a specific diagnosis. Some systemic autoimmune diseases, such as sarcoidosis, Sjögren syndrome, systemic lupus erythematosus, and IgG4-RSD, may include autoimmune TIN as a manifestation of disease. Occasionally, the systemic disease is unrecognized at the time of renal biopsy. In these patients, the recognition of an autoimmune etiology for TIN aids in diagnosis of that particular systemic disease and can guide therapy.

In this series, we describe the clinical and pathologic features in 35 kidney specimens, including 30 patients not previously described. In most of these patients, TIN as part of IgG4-RSD shows some unusual features not typically encountered in

other forms of TIN: in particular, TBM immune complex deposits, a moderate to marked increase in IgG4-positive plasma cells, elevated serum total IgG and/or IgG4 levels or hypergammaglobulinemia, and peculiar radiographic findings (low-attenuation renal lesions, often multiple and bilateral, or diffuse marked enlargement of kidneys). A combination of these features, in conjunction with clinical history suggestive of a systemic inflammatory disease, allows one to make a diagnosis of IgG4-TIN.

We examined the utility of the IgG4 stain in distinguishing IgG4-TIN from other forms of TIN with increased plasma cells. In the pancreas, increased IgG4+ plasma cells distinguish inflammatory infiltrates of AIP from those associated with other conditions.¹⁸ We surveyed an unbiased series of TIN biopsy patients from 1 year for increased plasma cells; an additional comparison group of specific types of plasma cell–rich infiltrates in the clinicopathologic differential diagnosis of IgG4-TIN was also included. One pitfall of IgG4 staining was that approximately 32% of pauci-immune GN tissue specimens showed at least moderately increased IgG4+ plasma cells. With the exclusion of pauci-immune GN tissue specimens, IgG4 staining in this series showed a high sensitivity and specificity for IgG4-TIN; additional clinical, radiographic, and laboratory features can contribute to increased certainty of the diagnosis, if these features are not suggestive of another cause of TIN.

One common feature in IgG4-TIN was TBM immune complex deposits. TBM deposits are unusual in TIN outside of interstitial inflammation associated with proliferative lupus nephritis and a subset of Sjögren syndrome patients, and were rarely present in our other control TIN tissue specimens. TBM deposits were more likely to be present in patients with expansile fibrosis (patterns B and C) than in those with an acute interstitial nephritis pattern (A), and TBM deposits were not found in areas away from those involved by interstitial inflammation. The TBM deposits thus may correlate with disease progression, although whether these deposits are causative of tubular injury or a result of inflammatory injury remains to be seen.

In this series of IgG4-TIN, 88% of patients showed elevated serum total IgG, IgG4, or hypergammaglobulinemia, including 79% with a known increase in serum IgG or IgG4. Similar findings have been reported in several studies of AIP in which 70 to 80% of patients show increased serum IgG or IgG4.¹⁹ Hamano *et al.* showed that the largest fraction of hypergammaglobulinemia in AIP was composed of IgG4,⁹ and so the presence of hypergammaglobulinemia in a patient with increased IgG4+ plasma cells on kidney biopsy may warrant further serologic testing for IgG and IgG4 levels. Eosinophilia was seen in 33% of our IgG4-TIN patients, and has been observed in AIP.²⁰ Eosinophilia may also be seen in acute allergic tubulointerstitial nephritis and thus may not be contributory without other clinical or radiographic features. Although these laboratory features can be helpful in making the diagnosis, their absence does not exclude the diagnosis of IgG4-TIN.

In some patients, IgG4-TIN may affect only the kidney at the time of renal biopsy. In the current series, six patients (17%) with IgG4-TIN had no other known organ involvement besides the kidney, although by definition for our series these patients had radiographic and/or laboratory features suggestive of IgG4 disease. It is conceivable that some patients may present with renal involvement of IgG4-RSD, with other clinical features becoming apparent later, or that some patients may have renal involvement only. An additional four biopsies not included in the IgG4-TIN group came from patients with no known other organ involvement, but had a histologic appearance unique to fibrotic IgG4-TIN. Given the histologic and immunophenotypic characteristics being similar to those with other organ involvement, these patients may represent sole renal involvement by IgG4 disease.

One entity in the differential diagnosis of IgG4-related TIN is so-called “idiopathic hypocomplementemic tubulointerstitial nephritis with extensive tubulointerstitial deposits”. A total of 12 patients of this hypocomplementemic TIN entity have been described in the literature.^{21–23} Many of these patients likely represent IgG4-TIN, as it was previously not widely recognized. Indeed, many of the described patients were elderly males. Two patients in the largest series of 8 biopsies had a history of sclerosing cholangitis, and one had leukocytoclastic vasculitis on skin biopsy, and so these three patients may represent IgG4-RSD or an overlap syndrome.

Also in the differential diagnosis of IgG4-TIN are Sjögren syn-

drome and lupus nephritis, both of which are systemic autoimmune diseases that may show interstitial inflammation and tubular basement membrane immune deposits on kidney biopsy. Similar to hypocomplementemic TIN, some patients diagnosed clinically as Sjögren syndrome may represent IgG4-RSD in the form of chronic sclerosing sialadenitis, which shows increased IgG4+ plasma cells.²⁴ Only 1 of 15 patients of Sjögren TIN in our control group showed increased IgG4+ plasma cells. Two of 10 lupus nephritis patients in our control group showed increased IgG4+ plasma cells. Lupus nephritis patients with TBM deposits can be distinguished histologically from IgG4-TIN by the usual presence of an accompanying proliferative immune complex GN. The presence of an additional glomerular disease or autoimmune condition, however, does not necessarily exclude the diagnosis of a concurrent IgG4-TIN.

We observed a range of histologic appearances of IgG4-TIN. One may speculate that these differences are related to the age of the lesion and represent different stages of disease: (A) acute interstitial nephritis with minimal fibrosis; (B) a more cellular inflammatory pattern in the setting of expansile fibrosis; and (C) a very fibrotic, pauci-cellular pattern. Two nephrectomy specimens, which allowed for examination of entire cross sections of mass lesions, showed denser fibrosis with less inflammation near the center of the mass and more inflammation resembling acute interstitial nephritis at the periphery, with the central fibrotic area representing the most long-lived area of an expanding mass lesion. Furthermore, the biopsy that showed the most severe fibrotic changes came from a patient with longstanding AIP, although the duration of renal involvement was unknown.

The standard medical therapy for AIP with pancreatic involvement is glucocorticoids. Patients typically show a marked response to prednisone or prednisolone, but there is a high relapse rate.²⁵ Less is known about the response to treatment in IgG4-related TIN. Saeki *et al.* showed a decrease in SCr at one month follow-up in most patients treated with prednisolone

Table 3. Proposed diagnostic criteria for IgG4-related TIN

Histology	Plasma cell-rich tubulointerstitial nephritis with >10 IgG4 + plasma cells/hpf field in the most concentrated field ^a Tubular basement membrane immune complex deposits by immunofluorescence, immunohistochemistry, and/or electron microscopy ^b
Imaging	Small peripheral low-attenuation cortical nodules, round or wedge-shaped lesions, or diffuse patchy involvement Diffuse marked enlargement of kidneys
Serology	Elevated serum IgG4 or total IgG level
Other organ involvement	Includes autoimmune pancreatitis, sclerosing cholangitis, inflammatory masses in any organ, sialadenitis, inflammatory aortic aneurysm, lung involvement, retroperitoneal fibrosis

Diagnosis of IgG4-TIN requires the histologic feature of plasma cell-rich TIN with increased IgG4 + plasma cells and at least one other feature from the categories of “imaging”, “serology”, or “other organ involvement”.

^aMandatory criterion.

^bSupportive criterion, present in >80% of cases.

who had an elevated SCr at presentation.¹³ We found a similar response rate to prednisone, sometimes combined with mycophenolate, in patients who had elevated SCr before treatment. Of note, even patients with markedly increased SCr and patients with diffuse interstitial fibrosis on biopsy showed a response to therapy, which may reflect steroid responsiveness of these fibrotic lesions, or perhaps the patchy nature of inflammatory lesions. Similar response rates have been published in the pancreatic literature in which a response to steroid treatment is typically seen within 2 weeks.²⁵

On the basis of this study, we propose diagnostic criteria for IgG4-TIN, based on histologic and immunophenotypic features, imaging, laboratory results, and other organ involvement. In addition to typical histology with a plasma cell–rich infiltrate (often with expansile interstitial fibrosis) and increased IgG4+ plasma cells, patients must have features from at least one other category including imaging (low-attenuation renal lesions or marked enlargement of kidneys), serology (elevated IgG or IgG4 levels), and other organ involvement by an inflammatory process. (See Table 3.) Pancreatic diagnostic criteria include response to steroids as a diagnostic criterion. Renal involvement differs from pancreatic involvement in IgG4-RSD, as many patients present with renal failure rather than, or in addition to, a mass lesion. Although IgG4-TIN responds in terms of SCr to steroid therapy, so do other types of TIN, and so steroid responsiveness is not deemed a diagnostic feature of IgG4-RSD in the kidney. Response to steroids of mass lesions in the kidney or in other organs, however, may help confirm the diagnosis.

In summary, IgG4-RSD is a distinct clinical entity with various patterns of organ involvement. As no single serologic or other test yet exists to diagnose this disease definitively, we rely on a combination of histologic, immunophenotypic, clinical, radiographic, and laboratory features to make the diagnosis. When this disease manifests in the kidney as TIN, the proposed criteria can distinguish IgG4-TIN from other types of TIN.

CONCISE METHODS

This study was approved by the Institutional Review Boards at Mayo Clinic and Massachusetts General Hospital; pathologic specimens originating at other institutions were reviewed at Mayo Clinic.

IgG4-TIN Patients

Patients were identified from Mayo Clinic, Nephropathology Associates, MA General Hospital, and Louisiana State University Health Sciences Center who had renal tissue findings of TIN and clinical, serologic, or radiographic features suspicious for IgG4-TIN ($n = 35$, including 5 patients previously reported¹²). To qualify as “suspicious” for IgG4-TIN, renal specimens must have shown a plasma cell–rich TIN and at least one of the following criteria: (1) Clinical evidence of other organ involvement by IgG4-RSD, (2) laboratory results of increased serum total IgG or IgG4 levels or hypergammaglobulinemia, or (3) radiographic features in the kidney of small peripheral cortical nodules, round or wedge-shaped lesions, or diffuse patchy involvement by computed tomography scan or magnetic resonance imaging

as described in AIP,¹⁵ or marked diffuse enlargement of kidneys by ultrasound.

Four additional specimens of TIN were identified that showed similar expansile plasma cell–rich TIN to patients with IgG4-RSD but did not qualify by our definition of suspicious for IgG4-TIN due to absence of data regarding other clinical, laboratory, or radiographic features. All four specimens showed a moderate to marked increase in IgG4+ plasma cells by IHC. One of these four specimens also showed concurrent MGN. These four specimens were deemed inconclusive for IgG4-TIN and were excluded from the statistical analyses. Two additional renal tissue specimens were identified from patients with a clinical history of IgG4-RSD; one showed MGN and the other showed renal cell carcinoma. These patients did not show a histologic pattern of TIN and were not included in the study.

Clinical data, presenting clinical, radiographic, and laboratory findings, medical history, treatment, and follow-up were obtained from referral forms submitted at the time of biopsy, patients’ medical records, and telephone interviews with the referring physicians. Laboratory results specifically sought were elevated total serum IgG and IgG4 levels (defined as >1590 mg/dl and >121 mg/dl, respectively), polyclonal hypergammaglobulinemia (>1.6 g/dl), peripheral blood eosinophilia (defined as counts $>0.5 \times 10^9$ per liter or $>5\%$ of peripheral white blood cells), serum C3 and C4 levels, ANCA, MPO, or PR3 antibodies, antinuclear antibody, anti–double-stranded DNA antibody, and studies for hepatitis B and C infection.

Control TIN Specimens

A database search of Mayo Clinic native renal biopsies was performed for all patients within 1 year (2007) with a final diagnosis of TIN, including some biopsies with associated glomerular disease. The cause of TIN in each patient was determined based on clinical and laboratory data. LM slides of all TIN patients were reviewed for increased plasma cells, defined for screening purposes as >5 cells per $\times 400$ magnification (hpf) in ≥ 3 fields. Those biopsies with increased plasma cells were stained for IgG4 by IHC (see below). Specific subtypes of TIN on biopsies done outside of the given year were also included: acute and/or chronic TIN in patients with a history of pancreatitis, pauci-immune GN, TIN in patients with Sjögren syndrome, proliferative lupus nephritis with interstitial inflammation and TBM deposits, drug-related TIN with increased plasma cells, chronic pyelonephritis, and unknown or possible autoimmune TIN with increased plasma cells. The Fisher exact test was used for statistical correlations; a P value of <0.05 was considered statistically significant; 95% confidence intervals were calculated for sensitivity and specificity using the Wilson score method without continuity correction.

Light Microscopy, Immunofluorescence, and Electron Microscopy

Standard processing for renal biopsies not performed for suspicion of tumor consisted of LM, IF, and EM. For LM, samples were stained with hematoxylin and eosin (H&E), periodic acid–Schiff, Masson’s trichrome, and Jones methenamine silver. For IF, 3- μ m cryostat sections were stained with polyclonal FITC conjugated antibodies to IgG, IgM, IgA, C3, C1q, kappa, lambda, fibrinogen, and albumin (Dako Corp., Carpinteria, CA). Biopsies and nephrectomies performed for

suspicion of tumor were routinely stained for H&E only. In IgG4-TIN specimens without material originally submitted for EM, EM was performed on deparaffinized tissue obtained from the light microscopy blocks, if sufficient tissue and blocks were available. LM slides were reviewed and IF and EM reports were reviewed on control biopsies; EM images were also reviewed in tissue specimens of IgG4-TIN.

Light microscopy slides were reviewed on all tissue specimens by a central pathologist (LDC). The interstitial nephritis was classified by the predominant pattern on the specimen as (A) acute interstitial nephritis with minimal fibrosis (<10% of cortex), (B) a more cellular inflammatory pattern in the setting of expansile fibrosis, and (C) a very fibrotic, pauci-cellular pattern. The degree of interstitial fibrosis and tubular atrophy was defined as mild ($\leq 25\%$), moderate (26 to 50%), or severe ($> 50\%$).

IgG4 Immunohistochemistry and IgG4 Grading

IHC was performed using the avidin-biotin complex-peroxidase method with monoclonal antibody to human IgG4 (Zymed, Carlsbad, CA; dilution 1:50 or 1:100 depending on staining laboratory) on sections from paraffin-embedded tissue. IgG4-positive plasma cells were counted per $\times 400$ magnification (hpf) and graded in the most densely concentrated area as follows: no increase < 5 cells per hpf, mild increase 5 to 10 cells per hpf, moderate increase 11 to 30 cells per hpf, and marked increase > 30 cells per hpf. IgG4 staining was performed on control TIN specimens with increased plasma cells and in TIN specimens in patients with clinical, serologic, or radiographic features suspicious for IgG4-TIN/IgG4-RSD.

ACKNOWLEDGMENTS

The authors acknowledge Dr. Andrew D. Rule, Mayo Clinic, for advice on statistics.

DISCLOSURES

None.

REFERENCES

- Deshpande V, Chicano S, Finkelberg D, Selig MK, Mino-Kenudson M, Brugge WR, Colvin RB, Lauwers GY: Autoimmune pancreatitis: A systemic immune complex mediated disease. *Am J Surg Pathol* 30: 1537–1545, 2006
- Kamisawa T, Funata N, Hayashi Y, Eishi Y, Koike M, Tsuruta K, Okamoto A, Egawa N, Nakajima H: A new clinicopathological entity of IgG4-related autoimmune disease. *J Gastroenterol* 38: 982–984, 2003
- Shrestha B, Sekiguchi H, Colby TV, Graziano P, Aubry MC, Smyrk TC, Feldman AL, Cornell LD, Ryu JH, Chari ST, Dueck AC, Yi ES: Distinctive pulmonary histopathology with increased IgG4-positive plasma cells in patients with autoimmune pancreatitis: Report of 6 and 12 cases with similar histopathology. *Am J Surg Pathol* 33: 1450–1462, 2009
- Zen Y, Kasahara Y, Horita K, Miyayama S, Miura S, Kitagawa S, Nakanuma Y: Inflammatory pseudotumor of the breast in a patient with a high serum IgG4 level: Histologic similarity to sclerosing pancreatitis. *Am J Surg Pathol* 29: 275–278, 2005
- Uehara T, Hamano H, Kawa S, Sano K, Honda T, Ota H: Distinct clinicopathological entity 'autoimmune pancreatitis-associated sclerosing cholangitis'. *Pathol Int* 55: 405–411, 2005
- Kitagawa S, Zen Y, Harada K, Sasaki M, Sato Y, Minato H, Watanabe K, Kurumaya H, Katayanagi K, Masuda S, Niwa H, Tsuneyama K, Saito K, Haratake J, Takagawa K, Nakanuma Y: Abundant IgG4-positive plasma cell infiltration characterizes chronic sclerosing sialadenitis (Kuttner's tumor). *Am J Surg Pathol* 29: 783–791, 2005
- Cheuk W, Chan JK: IgG4-related sclerosing disease: A critical appraisal of an evolving clinicopathologic entity. *Adv Anat Pathol* 17: 303–332, 2010
- Sarles H, Sarles JC, Muratore R, Guen C: Chronic inflammatory sclerosis of the pancreas—an autonomous pancreatic disease? *Am J Dig Dis* 6: 688–698, 1961
- Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, Fukushima M, Nikaido T, Nakayama K, Usuda N, Kiyosawa K: High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med* 344: 732–738, 2001
- Hamano H, Kawa S, Ochi Y, Unno H, Shiba N, Wajiki M, Nakazawa K, Shimojo H, Kiyosawa K: Hydronephrosis associated with retroperitoneal fibrosis and sclerosing pancreatitis. *Lancet* 359: 1403–1404, 2002
- Deshpande V, Mino-Kenudson M, Brugge W, Lauwers GY: Autoimmune pancreatitis: More than just a pancreatic disease? A contemporary review of its pathology. *Arch Pathol Lab Med* 129: 1148–1154, 2005
- Cornell LD, Chicano SL, Deshpande V, Collins AB, Selig MK, Lauwers GY, Barisoni L, Colvin RB: Pseudotumors due to IgG4 immune-complex tubulointerstitial nephritis associated with autoimmune pancreatocentric disease. *Am J Surg Pathol* 31: 1586–1597, 2007
- Saeki T, Nishi S, Imai N, Ito T, Yamazaki H, Kawano M, Yamamoto M, Takahashi H, Matsui S, Nakada S, Origuchi T, Hirabayashi A, Homma N, Tsubata Y, Takata T, Wada Y, Saito A, Fukase S, Ishioka K, Miyazaki K, Masaki Y, Umehara H, Sugai S, Narita I: Clinicopathological characteristics of patients with IgG4-related tubulointerstitial nephritis. *Kidney Int* 78: 1016–1023
- Watson SJ, Jenkins DA, Bellamy CO: Nephropathy in IgG4-related systemic disease. *Am J Surg Pathol* 30: 1472–1477, 2006
- Takahashi N, Kawashima A, Fletcher JG, Chari ST: Renal involvement in patients with autoimmune pancreatitis: CT and MR imaging findings. *Radiology* 242: 791–801, 2007
- Chari ST, Smyrk TC, Levy MJ, Topazian MD, Takahashi N, Zhang L, Clain JE, Pearson RK, Petersen BT, Vege SS, Farnell MB: Diagnosis of autoimmune pancreatitis: The Mayo Clinic experience. *Clin Gastroenterol Hepatol* 4: 1010–1016; quiz 1934, 2006
- Otsuki M, Chung JB, Okazaki K, Kim MH, Kamisawa T, Kawa S, Park SW, Shimosegawa T, Lee K, Ito T, Nishimori I, Notohara K, Naruse S, Ko SB, Kihara Y: Asian diagnostic criteria for autoimmune pancreatitis: Consensus of the Japan-Korea Symposium on Autoimmune Pancreatitis. *J Gastroenterol* 43: 403–408, 2008
- Zhang L, Notohara K, Levy MJ, Chari ST, Smyrk TC: IgG4-positive plasma cell infiltration in the diagnosis of autoimmune pancreatitis. *Mod Pathol* 20: 23–28, 2007
- Sah RP, Chari ST: Serologic issues in IgG4-related systemic disease and autoimmune pancreatitis. *Curr Opin Rheumatol* 23: 108–113
- Sah RP, Pannala R, Zhang L, Graham RP, Sugumar A, Chari ST: Eosinophilia and allergic disorders in autoimmune pancreatitis. *Am J Gastroenterol* 105: 2485–2491
- Kambham N, Markowitz GS, Tanji N, Mansukhani MM, Orazi A, D'Agati VD: Idiopathic hypocomplementemic interstitial nephritis with extensive tubulointerstitial deposits. *Am J Kidney Dis* 37: 388–399, 2001
- Gupta A, Jothy S, Somerville P, Zaltzman JS: Hypocomplementaemic immune complex tubulointerstitial nephritis. *NDT Plus* 3: 78–80, 2010
- Vaseemuddin M, Schwartz MM, Dunea G, Kraus MA: Idiopathic hypocomplementemic immune-complex-mediated tubulointerstitial nephritis. *Nat Clin Pract Nephrol* 3: 50–58, 2007
- Geyer JT, Ferry JA, Harris NL, Stone JH, Zukerberg LR, Lauwers GY, Pilch BZ, Deshpande V: Chronic sclerosing sialadenitis (Kuttner tumor) is an IgG4-associated disease. *Am J Surg Pathol* 34: 202–210, 2010
- Khosroshahi A, Stone JH: Treatment approaches to IgG4-related systemic disease. *Curr Opin Rheumatol* 23: 67–71, 2011