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Original Articles

Light-microscopic characteristics of IgG4-related tubulointerstitial nephritis: distinction from non-IgG4-related tubulointerstitial nephritis

Kazuhiro Yoshita[1,*], Mitsuhiro Kawano[2,*], Ichiro Mizushima[2], Satoshi Hara[2], Yumi Ito[1], Naofumi Imai[1], Mitsuhiro Ueno[3], Shinichi Nishi[4], Hideki Nomura[5], Ichiei Narita[1] and Takako Saeki[6]

[1]Division of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan, [2]Division of Rheumatology, Department of Internal Medicine, Kanazawa University Hospital, Kanazawa, Japan, [3]University Health Center, Joetsu University of Education, Joetsu, Japan, [4]Division of Nephrology and Kidney Center, Kobe University Graduate School of Medicine, Kobe, Japan, [5]Department of General Medicine, Kanazawa University Hospital, Kanazawa, Japan and [6]Department of Internal Medicine, Nagaoka Red Cross Hospital, Nagaoka, Japan

Correspondence and offprint requests to: Takako Saeki; E-mail: saekit@nagaoka.jrc.or.jp
*Both authors contributed equally to this work.

Abstract

Background. IgG4-related disease is a multi-organ disorder characterized by a high level of serum IgG4 and dense infiltration of IgG4-positive cells into affected organs. In routine studies, however, IgG subclasses are not estimated. In the present study, we attempted to clarify the light-microscopic characteristics of IgG4-related tubulointerstitial nephritis (TIN) to facilitate distinction from non-IgG4-related TIN in specimens obtained by renal biopsy using routine staining.

Methods. In specimens from 34 cases of TIN (13 IgG4-related and 21 non-IgG4-related), 9 nephrologists independently reviewed the following histological features of interstitial lesions: (i) cell infiltration extending into the renal capsule, (ii) cell infiltration into the renal medulla, (iii) regional lesion distribution, (iv) lymphoid follicles, (v) granulomatous lesions, (vi) necrotizing angiitis, (vii) eosinophil infiltration, (viii) neutrophil infiltration, (ix) tubulitis, (x) peritubular capillaritis, (xi) storiform fibrosis and (xii) the stage of interstitial fibrosis. The modified nominal group technique was applied to obtain a consensus in the pathological interpretation.

Results. Consensus was successfully attained among the diagnosticians for all but one pathological feature (regional lesion distribution). Storiform fibrosis was demonstrated in 12 of 13 (92.3%) cases of IgG4-related TIN but in none of the cases of other types of TIN. Cell infiltration extending into the renal capsule was also observed only in IgG4-related TIN. Conversely, neutrophil infiltration, severe tubulitis, severe peritubular capillaritis, granulomatous lesions and necrotizing angiitis were evident only in non-IgG4-related TIN.

Conclusions. This study revealed some useful and characteristic features for distinguishing IgG4-related from non-IgG4-related TIN on the basis of light-microscopic observation.

Keywords: IgG4; light microscopy; storiform fibrosis; tubulointerstitial nephritis

Introduction

IgG4-related disease (IgG4-RD) is a new clinical entity that has been attracting worldwide attention, being characterized by a high level of serum IgG4 and dense infiltration of IgG4-positive cells into affected organs [1–3]. The prototype of this condition was sclerosing pancreatitis [4] (also known as Type 1 autoimmune pancreatitis [5]), but it is known to affect various organs including the salivary glands, hepatobiliary tract, lymph nodes, lungs, retroperitoneum and kidneys [1, 2, 6, 7]. Recently, we reported that the major renal parenchymal lesion associated with IgG4-RD is tubulointerstitial nephritis (TIN) [8]. Because steroid therapy is usually quite effective, diagnosis of IgG4-related TIN is important. However, IgG4-related TIN is difficult to recognize in the absence of autoimmune pancreatitis or Mikulicz's disease, which are representative conditions of the disease [1–3] because serum IgG subclasses are not examined routinely and immunostaining for IgG subclasses is not a routine part of renal pathologic studies. Furthermore, recent studies have revealed that high serum IgG4 levels and/or IgG4-positive plasma cells can also be present in some inflammatory conditions that are not associated with IgG4-RD.

including anti-neutrophil cytoplasmic autoantibodies (ANCA)-associated vasculitis [9–11]. On the other hand, several studies have revealed that certain common pathological features of IgG4-RD are evaluable in routine examinations, such as storiform fibrosis, eosinophilic infiltration, lymphoid follicles and obliterative phlebitis, and that these are also useful for diagnosis [5–8, 12–16]. In fact, we have observed that some pathological features including storiform fibrosis in IgG4-related TIN were similar to those observed in Type 1 autoimmune pancreatitis [8]. However, it is still unclear whether the pathological features of IgG4-related TIN are actually characteristic in comparison with those of non-IgG4-related TIN and whether a consensus can be obtained among diagnosticians in the interpretation of pathological features such as storiform fibrosis, because tubulointerstitial lesions have not been fully examined from this perspective in ordinary TIN. These background factors prompted us to examine the light-microscopic characteristics of IgG4-related TIN, in which pathological consensus is attainable among diagnosticians, to allow its distinction from non-IgG4-related TIN using routine staining.

Materials and methods

Patients

This study included 13 patients with IgG4-related TIN (IgG4 group) and 21 patients with the other types of TIN (non-IgG4 group). The cases in both groups were selected from the renal biopsy pathology files at the Division of Clinical Nephrology, Niigata University (including cases seen at Nagaoka Red Cross Hospital) and the Division of Rheumatology, Kanazawa University Hospital, between 1998 and 2010 (IgG4 group) and between 2004 and 2010 (non-IgG4 group), respectively. Cases in which the specimens included over 100 glomeruli (obtained by surgery, open biopsy or autopsy) were excluded. The diagnosis of IgG4-related TIN was based on both (i) a high serum IgG4 level (>135 mg/dL) [17] and (ii) infiltration of numerous IgG4-positive plasma cells into the renal interstitium (IgG4-positive plasma cells/IgG-positive plasma cells >40% and/or IgG4-positive plasma cells >10/high power field), along with clinical features [18, 19]. The patients in the IgG4 group were all Japanese (11 males and 2 females) with an average age of 69.2 years (range 55–83 years). Twelve of the 13 patients had some IgG4-related extrarenal lesions (autoimmune pancreatitis, sialadenitis, dacryoadenitis, lymph node swelling, lung lesion, prostatitis or pseudo-tumor of the liver). The serum creatinine levels were within the range 0.9–6.17 mg/dL (average 2.55 ± 1.89). The levels of serum IgG4 before steroid therapy were 486–1860 (mean 1091, normal range <105). Hypocomplementemia was evident in 61.5% of the patients. None of them met the criteria for systemic lupus erythematosus, ANCA-associated vasculitis or sarcoidosis. Nine of the 13 patients had been included in our earlier study [8] and four were newly enrolled and had not been previously described.

The patients in the non-IgG4 group had a main renal pathological diagnosis of TIN, excluding IgG4-related TIN, renal allograft rejection and TIN associated with progressive chronic primary glomerular disease. The etiology of TIN included drug use (n= 6), vesicoureteral reflux (n= 1), malignant hypertension (n = 1), sarcoidosis (n = 2), Sjögren's syndrome (n = 3), ANCA-related vasculitis (n = 3) and idiopathic (n = 5). They were all Japanese (11 males and 10 females) with an average age of 55.7 years (range 11–80 years). Sialadenitis was present in three patients with Sjögren's syndrome and a patient with sarcoidosis showed lung lesions. The other 17 patients had no extra-renal lesions. Serum creatinine levels were 0.96–14.4 mg/dL (average 3.52 ± 3.07). Serum IgG4 levels were examined in three patients (two idiopathic and one Sjögren's syndrome) and were within the normal range in all of them. No patient showed hypocomplementemia. In all cases of idiopathic TIN, immunostaining for IgG4 revealed no or only few IgG4-positive plasma cells in the renal interstitium (data not shown).

Histological evaluation

Renal tissues were obtained by needle biopsy from all patients, except one patient with vesicoureteral reflux. For routine light-microscopic studies, renal biopsy specimens were fixed in formalin or alcohol-Bouin, embedded in paraffin and stained with hematoxylin and eosin, periodic acid-Schiff, periodic acid-methenamine silver (PAM) and Masson's trichrome or Azan. All tissue slides were anonymized and reviewed independently by nine nephrologists (all experts in renal pathology and routinely involved in the diagnosis of renal biopsy samples), who were blinded to the clinical and serological data and the IgG4/non-IgG4 status of the patients.

The estimated items pertaining to histological features were decided on the basis of previous pathological studies of IgG4-RD [5–8, 12–16]: (i) cell (inflammatory cell) infiltration extending into the renal capsule (absent, present or not evaluable due to lack of a renal capsule in the specimens), (ii) cell (inflammatory cell) infiltration into the renal medulla (absent, present or not evaluable due to lack of a renal medulla in the specimens), (iii) regional lesion distribution, well defined and excluding small patchy lesions (absent or present), (iv) lymphoid follicles with germinal centers (absent or present), (v) granulomatous lesions (absent or present), (vi) necrotizing angiitis (absent or present), (vii) eosinophil infiltration (0, no; 1 +, occasional and 2 +, numerous), (viii) neutrophil infiltration (0, no; 1 +, occasional and 2 +, numerous), (ix) tubulitis (0, no inflammatory cells in tubules; 1, mild; 1–4 cells per tubule cross section; 2, moderate; 5–10 cells per tubule cross section; 3, severe; >10 cells per tubule cross section, judged from the highest number of all types of cells infiltrating each tubule in the whole specimen), (x) peritubular capillaritis (0, no; 1, mild; 2, moderate; 3, severe; assigned a 'ptc' score of 0–3 in the Banff 07 classification [20]), (xi) storiform fibrosis (absent or present), (xii) stage of interstitial fibrosis (0, no fibrosis; 1, mild; scattered fibrosis; 2, moderate; degree of fibrosis less predominant than that of cell infiltration; 3, severe; degree of fibrosis more predominant than that of cell infiltration; 4; only fibrosis). In each specimen, all stages and the main stage were described respectively.

'Storiform fibrosis' is a characteristic swirling pattern of fibrosclerosing inflammation consisting of inflammatory cells and irregular fibrosis evident in Type 1 autoimmune pancreatitis [12]. In our earlier study, we demonstrated a similar pattern of fibrosis in IgG4-related TIN and showed that the irregular fibrosis surrounded nests of inflammatory cells in PAM-stained preparations [8]. In the present study, we defined 'storiform fibrosis in IgG4-related TIN' as a pattern of fibrosclerosing inflammation consisting of both (i) dense collagen fibers, into which inflammatory cells had infiltrated, exhibiting a swirling or arabesque pattern in the renal interstitium and (ii) irregular fibers surrounding nests of inflammatory cells in PAM-stained preparations. Representative photographs of storiform fibrosis in IgG4-related TIN are shown in Figure 1. Reference photographs of the stages of interstitial fibrosis (Stage 4 was not evident in any of the cases examined) are shown in Figure 2. Storiform fibrosis was evaluable in Stages 2 and 3. In our earlier study of IgG4-related TIN [8], obliterative phlebitis was not evident although phlebitis was shown in some patients (data not shown). Therefore, obliterative phlebitis was not investigated in this study.

The modified nominal group technique developed by the RAND Corporation [21] was applied to obtain consensus in the histopathological interpretation of renal biopsy specimens among the nine nephrologists. Briefly, each nephrologist recorded his/her assessments according to the rating system for TIN described later. These ratings were collected centrally, and the most frequent ratings were chosen as tentative interpretations. Then, the nephrologists anonymously rated the tentative interpretations on a 9-point scale, in which 1 = extremely inappropriate, 5 = uncertain and 9 = extremely appropriate. After anonymous feedback of the distribution of the ratings made by their colleagues and anonymous discussion via electronic mail, a second round of ratings was undertaken confidentially for all specimens regardless of the initial degree of agreement. To determine the final degree of agreement and disagreement, a statistical definition using a binomial distribution was applied. Consensus was considered to exist when no more than two individuals rated a particular indication outside a 3-point range (i.e. 1–3, 4–6 and 7–9). Items for which the nine nephrologists were unable to reach an agreement were discussed further in a group meeting. Attempts were made to modify the wordings of the rating system, and subsequently the third anonymous rating round was undertaken for these particular items. If a consensus was still not attainable after the third round of ratings, the item was described as 'consensus failure'.

Results

Renal pathology

The histological features of the IgG4 and non-IgG4 groups are summarized in Table 1. Consensus was successfully attained among the nine nephrologists for all but one pathological feature (a regional lesion distribution) in two cases. The features that were evident only in the IgG4 group were storiform fibrosis and 'cell infiltration extending into the renal capsule'. Storiform fibrosis was evident in 12/13 patients (92.3%) in the IgG4 group but in none of the non-IgG4 group (P < 0.0001) (Figure 3). Cell infiltration extending into the renal capsule, although this feature was not evaluable in many patients in the both groups, was evident in two patients in the IgG4 group (Figure 4). Conversely, neutrophil infiltration, granulomatous lesions and necrotizing angiitis were evident only in the non-IgG4 group [neutrophil infiltration = 12/21 (P = 0.0010), granulomatous lesions = 5/21 (P = 0.1317) and necrotizing angiitis = 5/21 patients (P = 0.1317)]. The grades of tubulitis were significantly lower in the IgG4 group (in the IgG4 group, stage of tubulitis was 0 in 7.7%, 1 in 76.9%, 2 in 15.4% and 3 in 0%, whereas in the non-IgG4 group, it was 0 in 0%, 1 in 33.3%, 2 in 47.6% and 3 in 19.0%, P = 0.0026). Severe tubulitis was evident only in the non-IgG4 group. Although the grades of peritubular capillaritis were not significantly different between the two groups, severe peritubular capillaritis was also evident only in the non-IgG4 group. A regional lesion distribution was observed more frequently in the IgG4 group (5/12 in the IgG4 and 1/20 in the non-IgG4, P = 0.0185); however, consensus in the pathological interpretation was not attainable in two patients. Cell infiltration into the renal medulla was observed in both groups (5/6 in the IgG4 and 12/15 in the non-IgG4, P = not significant). Eosinophil infiltration was evident in 30.8% of the patients in the IgG4 group and 9.5% in the non-IgG4 group, but the difference was not significant. Lymphoid follicles were evident in only one patient in the non-IgG4 group.

The results of interstitial fibrosis staging are summarized in Table 2. The stages of fibrosis were mixed in most cases in both groups. The IgG4 group had significantly higher stages of fibrosis than the non-IgG4 group (in the IgG4 group, main stage of fibrosis was mild in 15.4%, moderate in 61.5% and severe in 23.1%, whereas in the non-IgG4 group, it was mild in 57.1%, moderate in 42.9% and severe in 0%, P = 0.0054).

Discussion

Although the etiology of IgG4-RD has not been elucidated, some common pathological characteristics of this
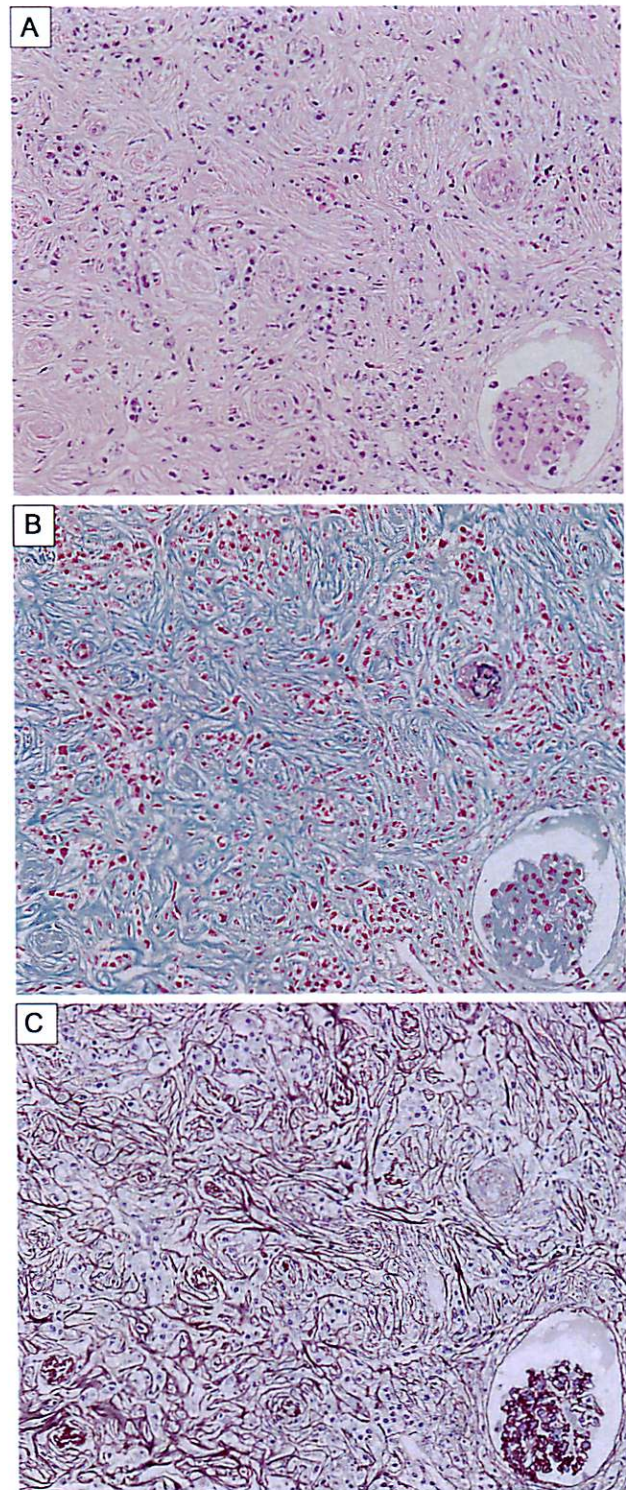

Fig. 1. Storiform fibrosis in IgG4-related TIN. A swirling or arabesque pattern consisting inflammatory cells and collagen fibers, corresponding to storiform fibrosis in Type 1 autoimmune pancreatitis, is evident (**A** and **B**). In PAM stain, irregular fibers surround nests of inflammatory cells (**C**). (**A**) Hematoxylin and eosin, (**B**) Elastica–Masson trichrome, (**C**) PAM. All images ×200 in almost the same field .

disease have been demonstrated. Dense lymphoplasmacytic infiltration with fibrosis and infiltration of numerous IgG4-positive plasma cells are the most characteristic
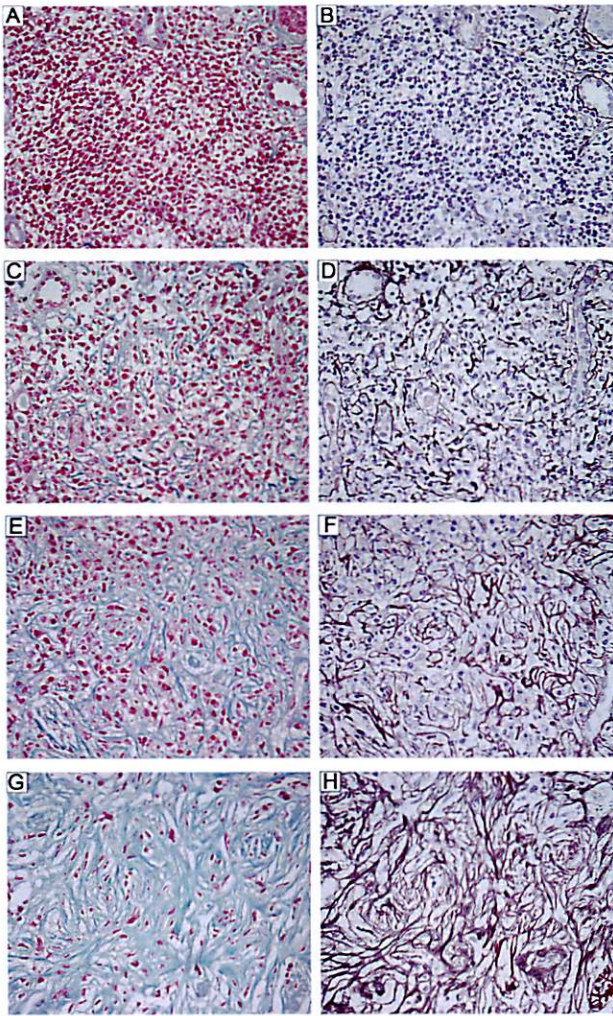
Fig. 2. The stages of interstitial fibrosis. Stage 0, no fibrosis (A and B); 1, mild; scattered fibrosis (C and D); 2, moderate; degree of fibrosis less predominant than that of cell infiltration (E and F); 3, severe; degree of fibrosis more predominant than that of cell infiltration (G and H). (A, C, E and G): Elastica–Masson trichrome, (B, D, F and H) PAM (×400). Each stage is from almost the same field in IgG4-related TIN.

features [1–8, 12–16, 18, 19] and storiform fibrosis, eosinophil infiltration, lymphoid follicles, inflammation around the margins of affected tissues, a regional lesion distribution and obliterative phlebitis have also been considered to be common features [5–8, 12–16, 22]. On the other hand, neutrophil infiltration and inflammation of the duct epithelium in affected organs are rare [7, 12, 13, 16]. In IgG4-related TIN, lymphoplasmacytic infiltration with numerous IgG4-positive plasma cells and fibrosis are also very important features [8]. Recently, Raissian et al. [18] revealed that the presence of plasma cell-rich TIN with numerous IgG4-positive plasma cells has diagnostic utility, with a sensitivity of 100% and specificity of 92%, for IgG4-related TIN, excluding pauci-immune necrotizing and crescentic glomerulonephritis. However, lymphoplasmacytic infiltration is a non-specific finding in TIN, and immunostaining is not performed routinely. Furthermore, recent studies have revealed that numerous IgG4-

positive plasma cells can also be present in conditions not associated with IgG4-RD [9–11]. Houghton et al. [9] described that the presence of numerous IgG4-positive plasma cells is essential to, but not sufficient for, the diagnosis of IgG4-related TIN. In addition, there is organ specificity in the pathological features of IgG4-RD [7]. For example, storiform fibrosis is not evident in the lymph nodes, minor salivary glands [7] or lung lesions [23]. It is important to examine the pathological findings closely in each organ and elucidate points of similarities and differences. In this study, we have revealed some useful and characteristic features for distinguishing IgG4-related from non-IgG4-related TIN on the basis of light-microscopic observation using routine staining, with consensus among diagnosticians. In particular, storiform fibrosis was revealed to be quite characteristic and useful for diagnosis of IgG4-related TIN. Because renal biopsy is usually applied to non-atrophic kidneys, dense interstitial fibrosis is noted relatively rarely in specimens obtained by biopsy. Interestingly, however, most of the patients with IgG4-related TIN showed high grades of fibrosis, even those with mild renal dysfunction, and the characteristic pattern was easy to recognize.

Cell infiltration extending into the renal capsule was evident in two patients in the IgG4 group. Because this feature is ordinarily not evident in other types of TIN, it might also be diagnostic of IgG4-related TIN. However, this feature was not evaluable in many of the patients in both groups, because specimens obtained by renal biopsy and subjected to light microscopy often lack the renal capsule. Therefore, further study to confirm this will be necessary. Neutrophil infiltration and severe tubulitis were not evident in IgG4-related TIN. Neutrophil infiltration has been described as rare in head and neck, hepatic and pancreatobiliary and retroperitoneal lesions in IgG4-RD [7]. Also, rarity of inflammation of the duct epithelium has been demonstrated in Type 1 autoimmune pancreatitis and IgG4-related sclerosing cholangitis [6, 12], suggesting these features are common in IgG4-RD. A regional lesion distribution was evident more frequently in the IgG4 group, suggesting that this may also be useful for the diagnosis of IgG4-related TIN. However, pathological interpretation of this feature was difficult in some patients, and a consensus could not be reached in two patients. Lymphoid follicles were evident in only one of all patients. Because specimens obtained by needle renal biopsy are quite small, lymphoid follicles with germinal centers might be difficult to discern. Eosinophil infiltration was often evident in IgG4-related TIN and so, IgG4-related TIN should be considered in the differential diagnosis of TIN with eosinophils. But there was no significant inter-group difference in this respect. Because eosinophil infiltration has also been reported as a common feature of non-IgG4-related TIN [24], it should be considered as not being diagnostic but rather a supportive feature of IgG4-related TIN. Granulomatous lesions and necrotizing angiitis, which are sometimes observed in sarcoidosis or ANCA-related vasculitis, were not evident in IgG4-related TIN, suggesting that they are useful features for distinguishing between these diseases, although

Table 1. Histological features of IgG4-related and non-IgG4-related TIN[a]

	IgG4 (*n* = 13)	Non-IgG4 (*n* = 21)	P
Cell infiltration extending into the renal capsule	2/7 (NE 6)	0/7 (NE 14)	0.4615
Cell infiltrations into the renal medulla	5/6 (NE 7)	12/15 (NE 6)	>0.9999
Regional lesion distribution	5/12 (CF 1)	1/20 (CF 1)	0.0185
Lymphoid follicles	0/13 (0%)	1/21 (4.8%)	>0.9999
Granulomatous lesions	0/13 (0%)	5/21 (23.8%)	0.1317
Necrotizing angiitis	0/13 (0%)	5/21 (23.8%)	0.1317
Storiform fibrosis	12/13 (92.3%)	0/21 (0%)	<0.0001
Eosinophil infiltration			
Grade 0	9/13 (69.2%)	19/21 (90.5%)	0.1084
Grade 1	3/13 (23.1%)	2/21 (9.5%)	
Grade 2	1/13 (7.7%)	0/21 (0%)	
Neutrophil infiltration			
Grade 0	13/13 (100%)	9/21 (42.9%)	0.0010
Grade 1	0/13 (0%)	9/21 (42.9%)	
Grade 2	0/13 (0%)	3/21 (14.3%)	
Tubulitis			
Grade 0	1/13 (7.7%)	0/21 (0%)	0.0026
Grade 1	10/13 (76.9%)	7/21 (33.3%)	
Grade 2	2/13 (15.4%)	10/21 (47.6%)	
Grade 3	0/13 (0%)	4/21 (19.0%)	
Peritubular capillaritis			
Grade 0	5/13 (38.5%)	5/21 (23.8%)	0.0649
Grade 1	5/13 (38.5%)	4/21 (19.0%)	
Grade 2	3/13 (23.1%)	8/21 (38.1%)	
Grade 3	0/13 (0%)	4/21 (19.0%)	

[a]NE, not evaluable; CF, consensus failure; grade of eosinophil and neutrophil infiltration: Grade 0, no; 1 +, occasional and 2 +, numerous; grade of tubulitis and peritubular capillaritis: Grade 0, no; 1, mild; 2, moderate and 3, severe.
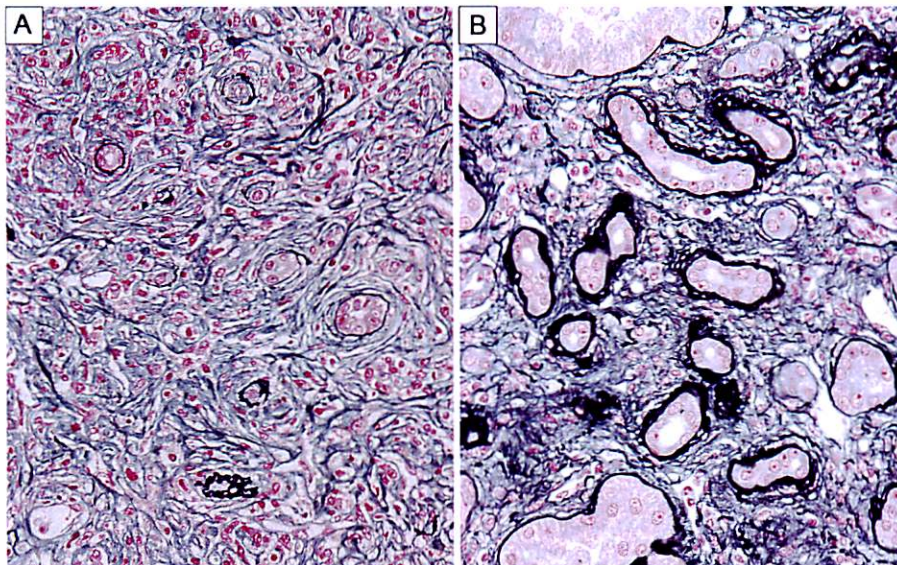

Fig. 3. Interstitial fibrosis of IgG4-related TIN and non-IgG4-related TIN. Characteristic storiform fibrosis is evident in IgG4-related TIN (**A**) but not in non-IgG4-related TIN (**B**) (PAM–Masson trichrome, ×400).

granulomas have rarely been observed in extra-renal organs associated with IgG4-RD [7].

Except for the items examined in this light-microscopic study using routine staining, immune complex deposits in the renal tubule basement membranes by immunofluorescence, immunohistochemistry and/or electron microscopy have been shown to be a characteristic feature of IgG4-related TIN [18, 25]. On the basis of these pathological features, nephrologists might be able to recognize

IgG4-related TIN in specimens obtained by renal biopsy using routine methods, even when no data for IgG subclass are available.

In this study, each item was examined closely by nine diagnosticians in a blinded manner, and a modified nominal group technique was used to elucidate whether consensus can be obtained among diagnosticians in the interpretation of pathological features. For this purpose, the study employed a relatively small cohort size, and
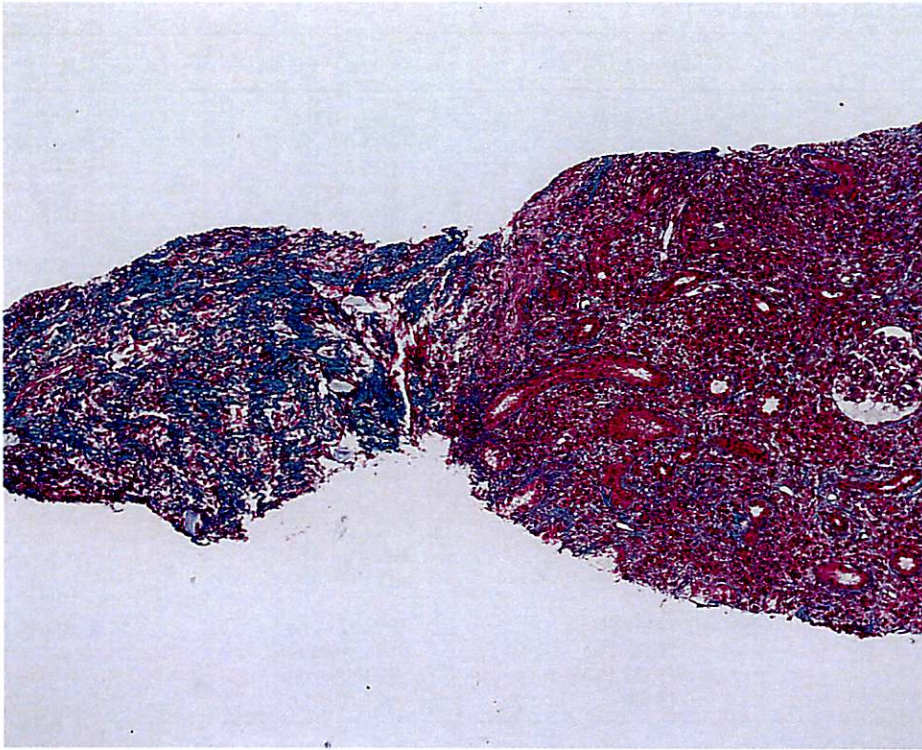
Fig. 4. Cell infiltration extending into the renal capsule. Inflammatory cells are evident within the renal capsule (Masson's trichrome, ×100).

Table 2. Stages of interstitial fibrosis of IgG4 and non-IgG4-related TIN[a]

	IgG4 ($n = 13$)	Non-IgG4 ($n = 21$)	P
Mean s-Cr (mg/dL) (range)	2.55 (0.9–6.17)	3.52 (0.96–14.4)	0.2719
Main stage			
1	2/13 (15.4%)	12/21 (57.1%)	0.0054
2	8/13 (61.5%)	9/21 (42.9%)	
3	3/13 (23.1%)	0/21 (0%)	
All stages			
0 + 1	1/13	1/21	
1	0/13	2/21	
0 + 1 + 2	0/13	4/21	
1 + 2	2/13[b]	5/21	
0 + 1 + 2 + 3	2/13[b]	3/21	
1 + 2 + 3	8/13[b]	6/21	

[a]s-Cr, serum creatinine; Stage 0, no fibrosis; 1, mild fibrosis; 2, moderate fibrosis and 3, severe fibrosis.
[b]Storiform fibrosis was evident.

addition of TIN cases proven to have non-IgG4 status as controls was unfortunately impossible. However, including more non-related TIN cases would make the P-values more significant for certain features (granulomatous lesion or necrotizing angiitis). Further studies employing a larger cohort size and including all types of TIN as a control will be necessary to clarify the positive and negative predictive values of each item for diagnosis of IgG4 TIN.

In conclusion, the present study identifies some useful and characteristic features for distinguishing IgG4-related TIN from non-IgG4-related TIN in specimens examined by light microscopy. However, the significance of these pathological findings and the etiology of IgG4-RD remain poorly understood. Further studies will be necessary to elucidate the underlying mechanisms.

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Timing of initiation of renal replacement therapy for acute kidney injury: a survey of nephrologists and intensivists in Canada

Edward Clark[1], Ron Wald[2], Michael Walsh[3,4] and Sean M. Bagshaw[5]; for the Canadian Acute Kidney Injury (CANAKI) Investigators*

[1]Kidney Research Centre, Ottawa Hospital Research Institute, University of Ottawa, Ottawa, Canada, [2]Division of Nephrology and Keenan Research Centre, Li Ka Shing Knowledge Institute, St. Michael's Hospital, University of Toronto, Toronto, Canada, [3]Division of Nephrology, Department of Medicine, McMaster University, Hamilton, Canada, [4]Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Canada and [5]Division of Critical Care Medicine, University of Alberta, Edmonton, Canada

Correspondence and offprint requests to: Sean M. Bagshaw; E-mail: bagshaw@ualberta.ca
*The Canadian Acute Kidney Injury (CANAKI) Investigators are listed in the acknowledgement section.

Abstract

Background. Little is known about factors that influence the timing of initiation of renal replacement therapy (RRT) for acute kidney injury (AKI). We sought to better describe these factors for Canadian physicians that prescribe RRT for AKI.
Methods. A web-based survey was conducted of physicians involved in the decision to initiate RRT for critically ill patients in Canada. Participants were asked about the factors that prompt them to initiate RRT for AKI both directly and using scenario-based questions.
Results. Surveys completed by 180 physicians at 32 different sites were included for analysis. Serum potassium level and severity of pulmonary edema were the most commonly utilized factors for deciding when RRT should be started. For all clinical and laboratory factors inquired about, there