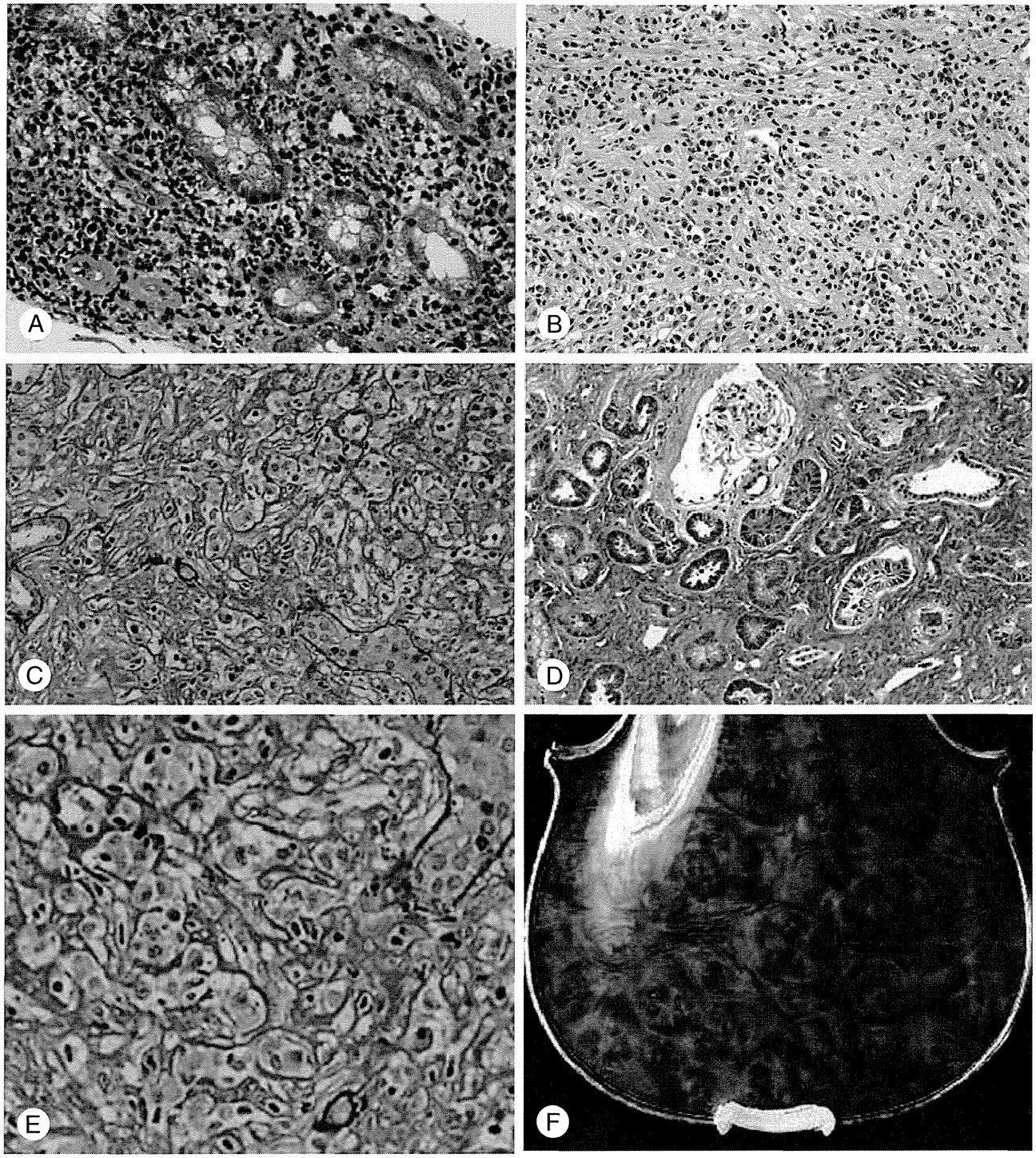
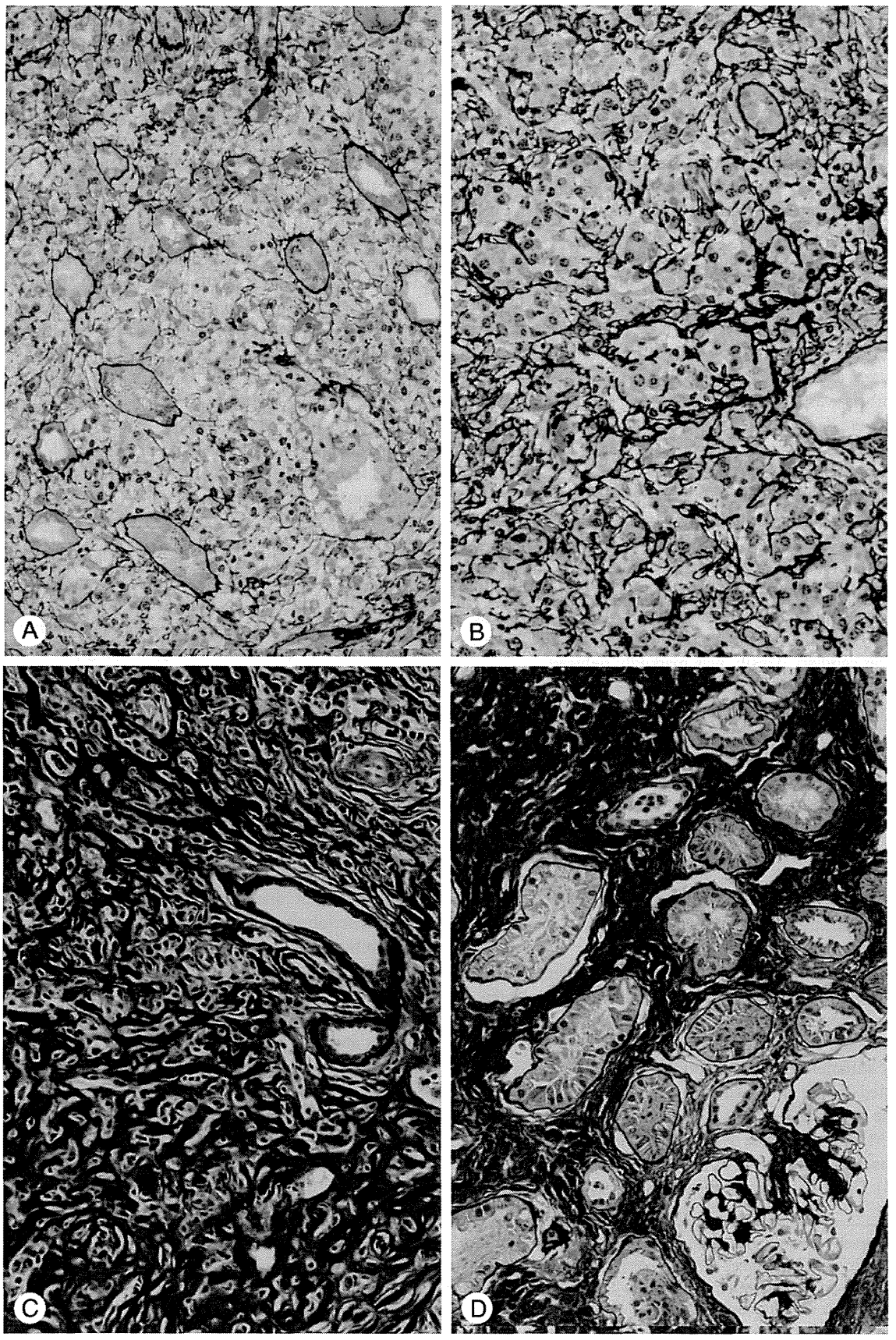



**Fig. 3** Various tubulointerstitial changes classified as stages (A to D). (A), Stage A: lymphoid cell–predominant interstitial infiltration with minimal tubulitis (hematoxylin and eosin [H&E] staining). (B), Stage B: plasma cell–predominant infiltration and scattered eosinophils with diffuse connective tissue deposition (H&E). (C), Stage C: small, swollen plasma cell nests encircled by collagenous tissue (PAS). (D), Stage D: diffuse collagen deposition widens the intertubular spaces. Note peculiar features showing nonatrophic tubuli, despite progressive fibrosis. (E), Large magnification of characteristic morphology of (C) showing a bird's-eye pattern (F). Original magnification: A, ×100; B, ×40; C, ×200; D, ×40; E, ×400.


A
B
C
D

inflammatory cell infiltrates often expanded into the spaces between the tubules and peritubular capillaries.

The cellular components of inflammatory infiltrates comprised plasma cells, lymphocytes, and variable numbers of eosinophils. The cellular composition of the inflammatory cells altered with progression of the fibrosis (Fig. 3A-D). Initially, when fibrosis is less apparent, lymphocytes as well as plasma cells are the predominant component, whereas plasma cells become more prominent in parallel with growing fibrosis. Inflammatory infiltrates attenuate when fibrosis extends. Fibrosis and inflammatory infiltrates were associated in most cases, but inflammatory infiltrates tended to accumulate at the margins of the solid lesions. Small nests of plasma cells or individual plasma cells were commonly encased by fibrosis. The features resembled a maple wood grain pattern called "bird's eye" (Fig. 3E and F). Such "bird's-eye" fibrosis was observed in all cases (100%). Lymphoid follicles were detected in 9 patients (45%; data not shown).

Because the degree of fibrosis was variable among the samples, we tentatively classified the stage of fibrosis as follows: stage A, active cellular infiltration with little fibrosis; stage B, active cellular infiltration with mild but distinct interstitial fibrosis; stage C, interstitial fibrosis dominant with mild cellular infiltration; and stage D, advanced interstitial fibrosis with little cellular infiltration (Fig. 4). In 15 cases (94%), different stages could be identified in a single specimen. Given that the interstitium was replaced by fibrosis, peritubular capillary density was markedly reduced.

Stages were better characterized by EM (Fig. 5). In the early stages, A to B (Fig. 5A), interstitial fibrosis revealed bundles of fine fibrils that were sparse among the infiltrating cells; however, with more advanced fibrosis, such as in stage C, fibrous bundles encased each interstitial inflammatory cell (Fig. 5B). In the advanced stage D, fibrous bundles became thick, and interstitial infiltrating cells were atrophic (Fig. 5C). Note that fibrils seemed to be low-dense and distinct fibers compared with those of earlier stages. On higher magnification, distinct collagen bundles were observed around the infiltrated fibroblastic cells, which were intermingled with inflammatory cells (Fig. 5D).

Additional characteristics noted in our series were nodular hyaline deposits on the tubular basement membrane (TBM) of atrophic tubules, found in 10 cases (63%; Fig. 6A), and under Bowman epithelium in 5 cases (31%). This lesion is sufficiently recognizable by LM, and the deposits are limited to the involved area, as revealed by Masson trichrome staining.

By EM, electron-dense deposits were seen in TBMs in 10 of 10 cases analyzed, and in Bowman capsules in 4 cases (Table 3). Deposits were prominent in the TBMs of atrophic tubules with a coarse granular pattern (Fig. 6B). Electron-dense deposits in the interstitium were detected in 7 cases. Dense deposits were occasionally noted in the perivascular areas. There were no distinct substructures in the deposits. In glomeruli, subepithelial deposits were detected in 3 cases, including 2 cases of membranous glomerulonephritis.

Immunofluorescence analysis was available in 5 cases, and others were examined with peroxidase-antiperoxidase methods in paraffin sections, the latter being inadequate to estimate interstitial immune deposition. In the 5 cases for which IF was available, all showed IgG, IgG1, and IgG4 deposition in the TBM and interstitium. IgG3 was found in 3 cases, whereas IgG2 was noted in 1. C3 was found in 3 cases, in interstitium, Bowman capsule, and the TBM. C4 and C1q were detected in 1 and 2 cases, respectively (Fig. 7). $\kappa$ or $\lambda$ light chains were equally stained, suggesting polyclonal immunoglobulin deposition (Table 4 and Fig. 8). The average proportion of IgG1-, IgG2-, IgG3-, or IgG4-positive plasma cells was 24.3%, 4.9%, 22.3%, or 48.5%, respectively, in 16 cases examined (Table 5). In stage A samples, predominant IgG4 immunostaining was evident among infiltrated plasma cells. The IgG subclass population in cases with and without AIP showed no statistical differences.

### 3.2.2. Glomerulus

Glomeruli generally showed minor abnormalities by LM. Glomerular collapse, occasionally showing presumable atubular glomeruli and global sclerosis, was observed in areas of extensive interstitial fibrosis. Two cases had concomitant membranous glomerulonephritis, as revealed by EM.

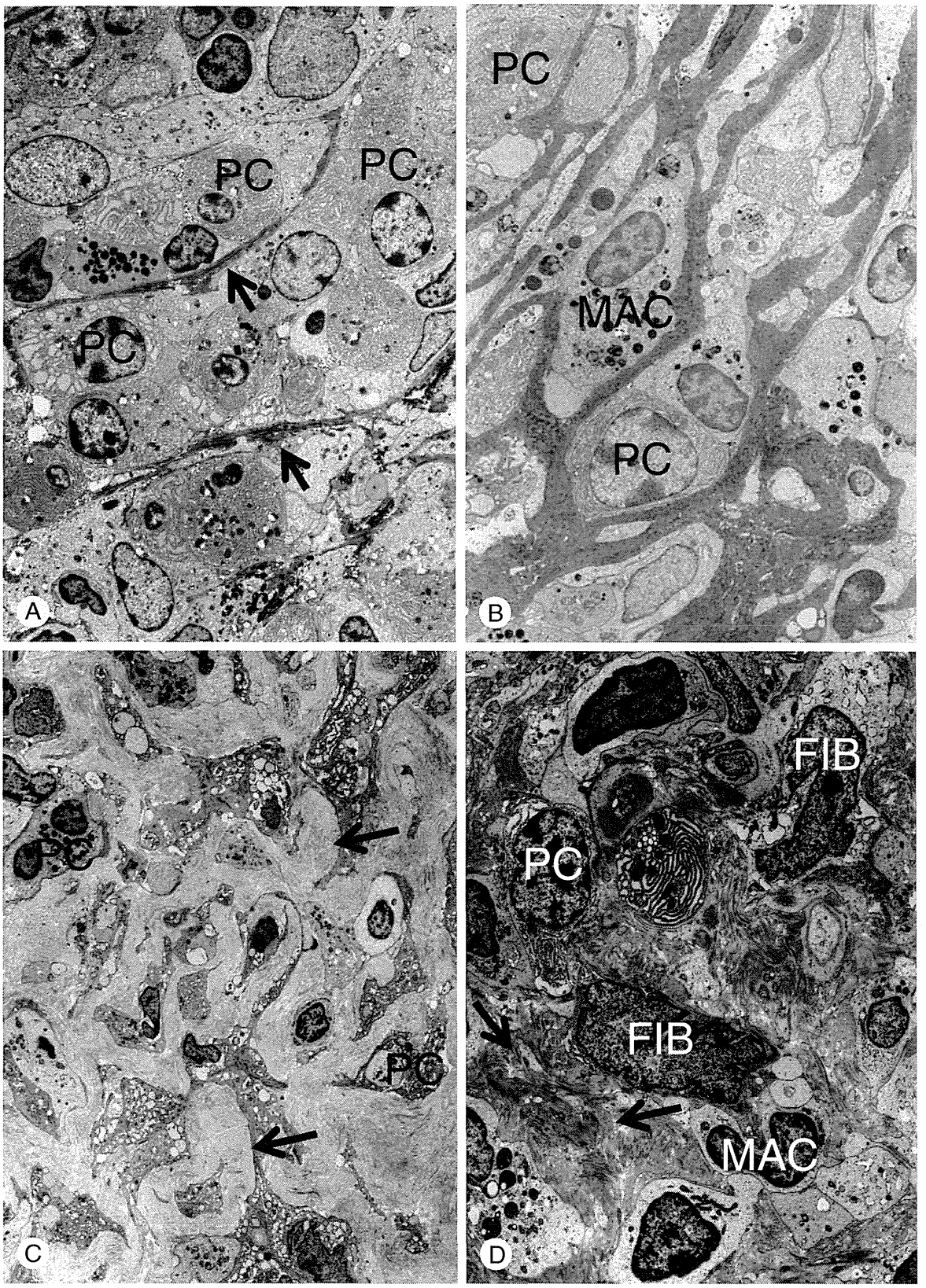
### 3.2.3. Vasculature

Vascular changes seemed to be associated with interstitial changes. In portions with advanced fibrosis, small arteries or arterioles revealed loss of vascular smooth muscle cells showing mucoid features. Onion skinning was also noted at the perivascular interstitium. Five cases showed phlebitis and/or interlobular venous sclerosis, but phlebosclerosis was not prominent. Cellular infiltration, fibrosis, and rupture of the external elastic lamina around the interlobular arteries and small arteries were observed, suggesting perivasculitis. These vascular changes occasionally comprised medial fibrosis and luminal narrowing.

## 4. Discussion

The present study characterized the pathologic features of 16 cases from across Japan that may prove useful in

**Fig. 4** Development of interstitial fibrosis and inflammatory retraction as revealed by the periodic acid methenamine silver stain (PAM stain). (A), Incipient appearance of PAM-positive thin fibers among inflammatory infiltrates corresponding to stage A. (B), Characteristic cell nests and PAM-positive fibrous bundle pattern demonstrate the bird's-eye pattern. (C), Increased interstitial PAM-stained fibrosis and pyknotic cell nuclei with scant cytoplasm. (D), Thick interstitial PAM-stained bundles among tubular spaces. Note that inflammatory infiltrates are minimal and tubuli are not atrophic. Original magnification: A, ×100; B, ×100; C, ×40; D, ×100.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distinguishing IgG4-related TIN from other types of TIN. First, a relatively well-demarcated border between involved and uninvolved areas was present. Second, lesions were not restricted to the cortex but often involved the deep medulla and the renal capsule as well. The latter occasionally extended to the peritoneal fibrosis. Third, plasma cell–predominant infiltration was frequently and prominently admixed with fibrosis in varying proportions—even in a single sample—with highest prevalence in the IgG4-positive cell fraction. Fourth, bird's-eye fibrosis was observed in all cases and is unique to this disease. Fifth, deposits in the TBM, Bowman capsule, and interstitium were present and were sufficiently identifiable by LM with periodic acid-Schiff (PAS) and Masson trichrome staining. These characteristics were similarly observed in cases with or without AIP, thus supporting an LM-based differential diagnosis from other types of TIN. Further studies testing interobserver validation and reproducibility should be done.

Although glomerular changes are sometimes associated with TIN in IgG4-related nephropathy [12,13,16,20], the histologic findings in our series showed that the tubulointerstitial changes are the main cause of progressive renal dysfunction.

Generally, TIN is defined by inflammatory infiltrates in the interstitium with frequent tubulitis [27]. Tubulointerstitial inflammation in IgG4-related TIN is composed mainly of lymphocytes and plasma cells with various numbers of eosinophils, but neutrophil infiltration is unremarkable [1,9,10,17,24]. Notably, the cases in our series very seldom manifested tubulitis, even in stage A, showing predominant inflammatory cell infiltration. In AIP, plasma cell–predominant infiltration, particularly frequent IgG4-positive cell infiltration, is an important diagnostic feature [2-4]. Likewise, IgG4-positive cells in the interstitium are typical features, provoking TIN [10-14,17-22]. Immunohistochemistry for IgG subclass–positive cells showed an elevation of the IgG4-positive cell population to 48.5%, on average. Interestingly, IgG4-positive cells remained as interstitial fibrosis progressed in stages C and D. Although IgG4-positive cells are substantially increased, IgG3-positive cells are also increased relative to normal kidney tissue, in which IgG3-positive cells are largely absent. This is the first report on IgG subclass populations in IgG4-related TIN; an involvement of other IgG subclass–positive cells in this type of TIN needs further investigation.

Steroid treatment has been reported to be effective in IgG4-related TIN. Although follow-up data are not shown in the present article, serial biopsy in case 15 revealed decreased IgG4-positive cell infiltration (from 41.5% to 18.2%) with progressive fibrosis after steroid treatment. However, IgG4-positive cell infiltration increased again (to 57%) after clinical recurrence after steroid discontinuation. More interestingly, reappearance of the bird's-eye pattern accompanied this change (data not shown). These findings imply that the various histologic features categorized by us as stages A to D reflect different disease stages, rather than histologic variations. In addition, we surmise that serum

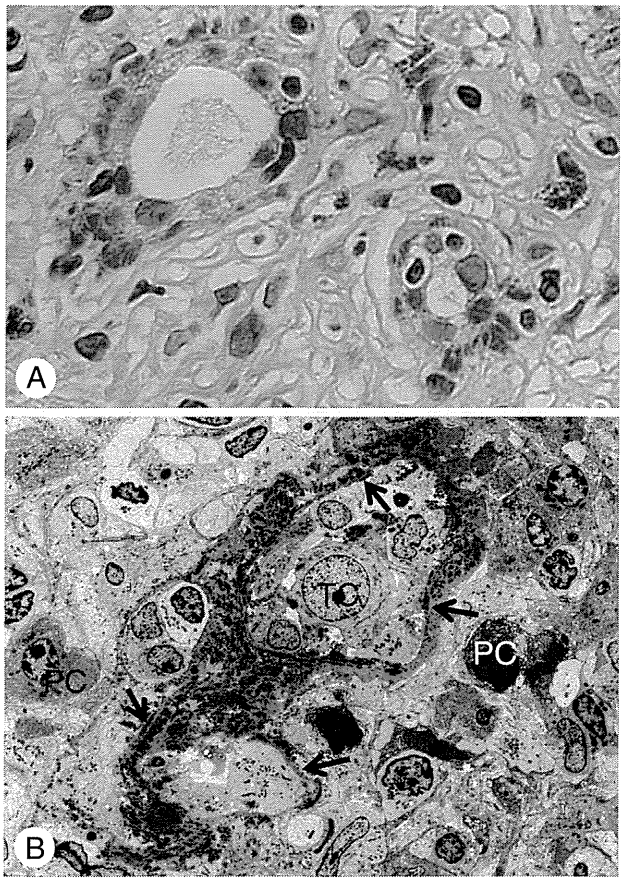


**Fig. 6** Tubulointerstitial depositions. (A), Apparent deposition (red) in the thickened TBM by Masson trichrome staining. (B), Granular electron-dense deposits (arrow) are accumulated in the thickened TBM but not apparent in the tubular cytoplasm. Note that the scattered particles of deposits are also observed in the interstitium. Original magnification: A, ×400; B, ×100. PC, plasma cell; TC, tubular cell.

**Fig. 5** Electron microscopic findings of different stages of fibrosis. (A), Stage A: thin fibrous deposition among lymphoplasmacytoid cells. (B), Stage B: fibrous deposition has become more extensive, and plasma cells and eosinophils have abundant cytoplasm with granules. (C), Stage C: deposition of intercellular fibrous bundles is thicker, and numbers of mononuclear cells are reduced and atrophic. (D), The presence of fibroblasts among the inflammatory cells is accompanied by dense fibrous bundles of interstitial-type collagen (all figures, original magnification ×1000). PC indicates plasma cells; FIB, fibroblasts; MAC, macrophage; arrow, collagen. Original magnification: A, ×2400; B, ×3600; C, ×1200; D, ×4800.

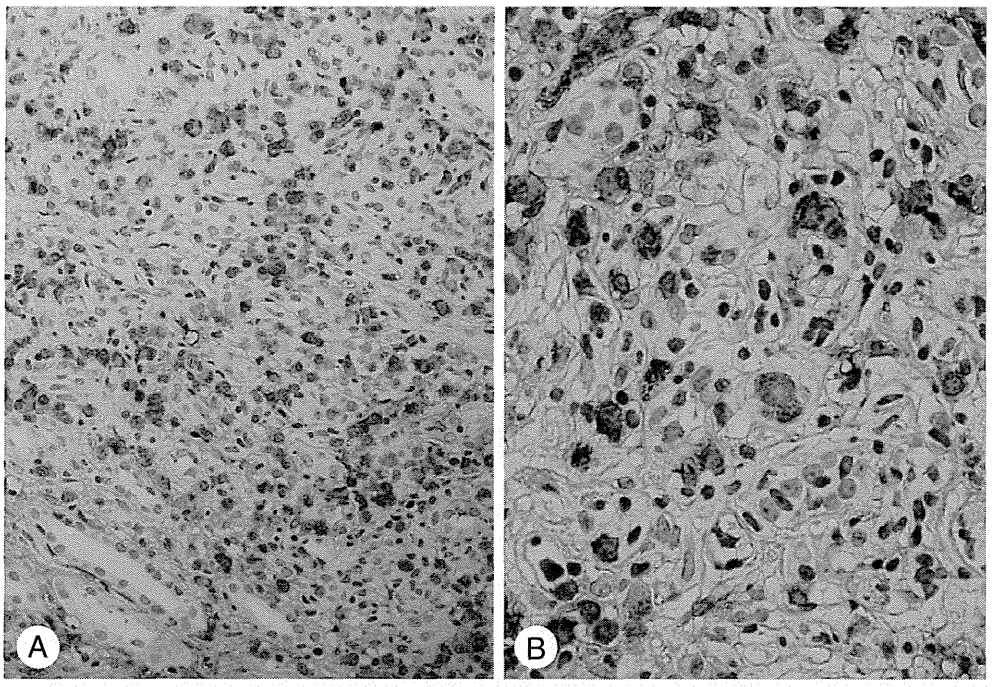


**Fig. 7** IgG4 immunostaining. (A), IgG4-positive cells among severe lymphoplasmacytic infiltration of Stage A. Note that relatively frequent IgG4-positive cells account for appro×imately 40% of the total infiltrating cells. (B), Larger magnification of IgG4-positive cells showing predominant cytoplasmic localization. Original magnification: A, ×100; B, ×400.

IgG4 levels may reflect a systemic increase of IgG4-positive cells because of a steroid-induced attenuating disease activity owing to suppression of IgG4-positive cells. The accumulation of rebiopsied cases with steroid treatment is needed to investigate this hypothesis.

The kidney is one of the susceptible organs in IgG4-related disease, although the underlying mechanisms are still unknown. Given the elevated plasma IgG4 levels, significant elevation of IgG4-positive cells, and electron-dense deposition in the pancreas, Deshpande et al [24] suggested an immune complex–mediated mechanism in AIP. Similarly, in the kidney, Cornell et al [10] found deposits in the TBM as well as in glomeruli in some cases, also suggestive of an immune complex disease. This is consistent with previous reports showing an association of the circulatory immune complex with nephropathy [13,19,28]. Our series of cases revealed interstitial deposition in all cases in which EM was performed. However, it is still unclear whether interstitial deposits are immune complexes.

Complement activation is one factor suggesting that deposition results from immune complex formation. Our IF study showed that IgG4 deposition in Bowman capsule, TBM, and interstitium was associated with C3 deposition. In addition, IgG4 deposition was associated with IgG and IgG1, and occasionally with IgG3. Notably, IgG4 alone has been reported to insufficiently activate the complement cascade [28]. Thus, it may be that complement activation is based on the presence of IgG1 or IgG3, but not IgG4.

The mechanism of intrarenal IgG4 deposition remains unexplained. Curiously, we noticed that deposits are limited to the affected tubulointerstitium, where IgG4-positive cells are present, but are not observed in the uninvolved portions. In addition, deposition is histologically associated with plasma cell infiltration. This suggests that interstitial IgG4 deposits may be derived from local production. Because IgG4 per se may not filtered in the glomeruli and cases with these deposits are not associated with glomerulopathy, tubular deposition may not be derived from IgG4 filtered in glomeruli and absorbed by the tubuli or Bowman epithelium. Accumulation of IgG4 in the Bowman capsule and TBM may require another mechanism.

Although interstitial fibrosis is associated with plasma cell infiltration as well as deposition, the present study cannot determine how deposition or plasma cell infiltration promotes progressive fibrosis. Characteristically observed as a bird's-eye pattern, fibrosis commences in the active inflammatory stage A as revealed by EM. In addition, fibrosis grows in the intercellular spaces among viable inflammatory cells. Electron microscopy in the present study clearly identified fibroblastic or myofibroblastic cells in interstitial-type collagen in both the cytoplasm and pericellular spaces. This suggests that fibroblasts are the culprits causing fibrosis. Interstitial fibrosis in typical TIN is based on tubulitis; however, it is unusual in IgG4-related TIN. This implies that progressive interstitial fibrosis in IgG4-related TIN may be mechanistically different from

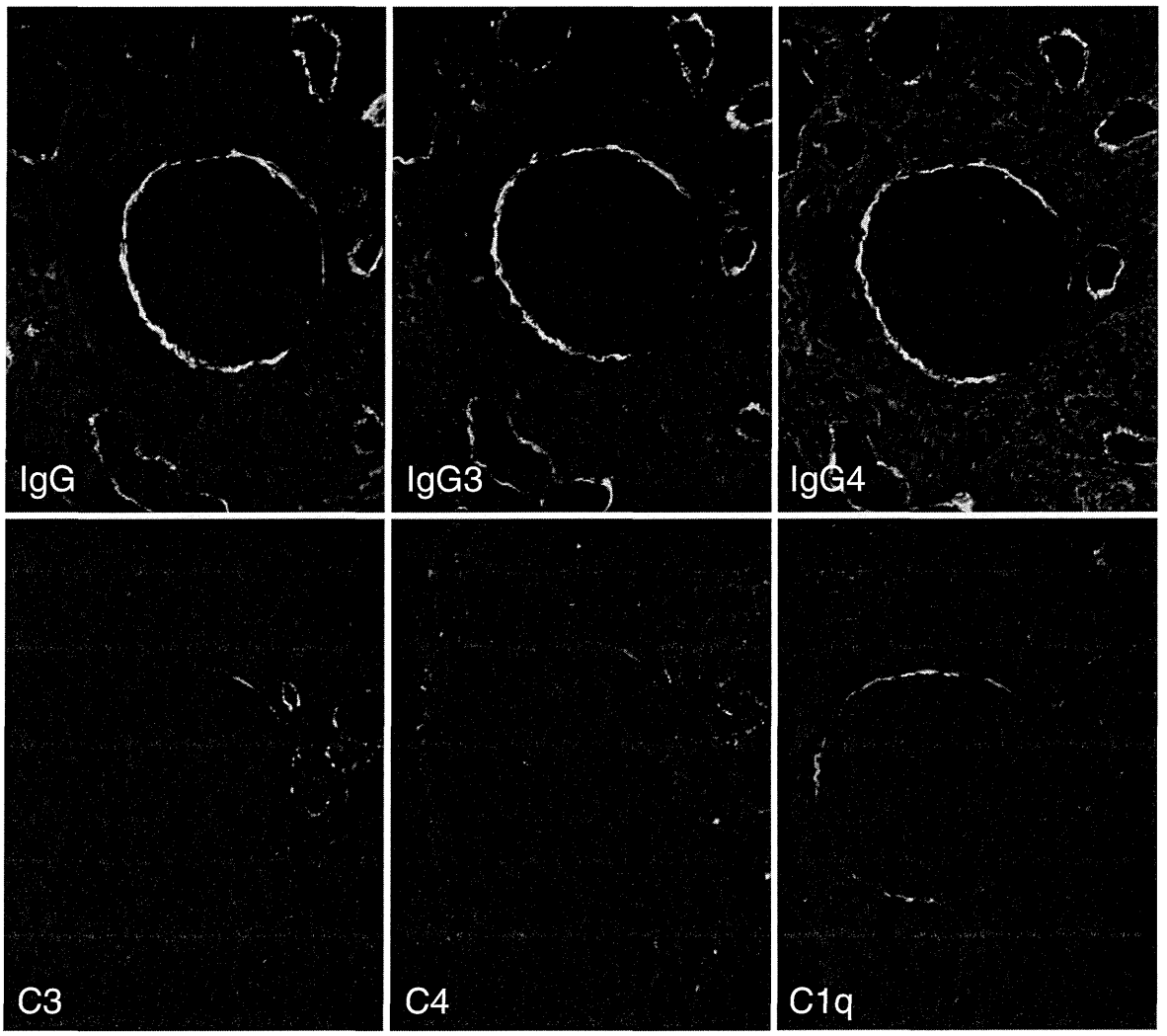


**Fig. 8** Immunofluorescence. Serial sections from case 10. In the upper panel, IgG, IgG3, and IgG4 reveal similar distributions. Notably, strong accumulation was observed in the Bowman capsule and TBM. Interstitial deposits are also observed. Lower panel shows complement deposition. Granular pattern deposition of C3 is found in some TBM and interstitium. C4 and C1q are faint but distinctly observed in TBM, but not in interstitium. Magnification: ×200.

that in TIN in general. As shown in our study, not only IgG4- but also IgG1- and IgG3-positive cells are substantially present in the interstitium. The local immune network, not restricted to IgG4, may be involved in fibrosis. Further study is required to identify the mechanism of fibrosis in IgG4-related TIN, particularly from the perspective of therapeutic strategy.

IgG4-related disease is a systemic disease, and TIN is not always associated with AIP. In particular, cases with abnormal kidney CT without AIP are sometimes misdiagnosed as renal tumors, and nephrectomy is performed. In such cases, pathologic evaluation only shows TIN or features of inflammatory pseudotumors. In this regard, the present study describes the characteristic histopathology of IgG4-related TIN, which is useful for differentiating TIN in general as well as making a diagnosis of TIN lesions in nontumor cases. In addition, we provide the first evidence that renal pathology in IgG4-related TIN with or without AIP is otherwise identical. Our observations should benefit differential diagnosis using renal biopsy, which is used in a variety of diseases.

## 5. Conclusion

This series of IgG4-related nephropathy cases in Japan show its distinctive pathology in relation to TIN. The features may be useful in identifying cases with IgG4-related nephropathy that are not associated with AIP or with systemic sclerosing diseases. The renal histology of IgG4-related nephropathy will be better clarified by accumulating more cases, particularly with repeat biopsies,

**Table 5** Percent positive cells in IgG subclasses staining

| Case | IgG1 | IgG2 | IgG3 | IgG4 |
|---|---|---|---|---|
| With AIP | | | | |
| 1 | 28.2 | 11.6 | 16.9 | 43.3 |
| 2 | 22.1 | 0.1 | 31.4 | 46.4 |
| 3 | 32.1 | 0.9 | 26.5 | 40.5 |
| 4 | 18.4 | 0.0 | 32.4 | 49.2 |
| 5 | 13.3 | 8.1 | 32.2 | 46.4 |
| 6 | 33.4 | 8.6 | 11.4 | 46.6 |
| 7 | 42.3 | 8.1 | 8.1 | 41.4 |
| 8 | 23.0 | 7.8 | 28.5 | 40.5 |
| | 27.1 ± 9.3 | 5.3 ± 4.6 | 22.7 ± 9.8 | 44.8 ± 3.3 |
| Without AIP | | | | |
| 9 | 16.9 | 1.0 | 32.9 | 49.2 |
| 10 | 22.8 | 0.0 | 23.0 | 54.2 |
| 11 | 33.7 | 11.0 | 10.0 | 45.3 |
| 12 | 11.0 | 1.1 | 24.2 | 63.7 |
| 13 | 15.7 | 4.1 | 28.9 | 51.3 |
| 14 | 32.3 | 0.0 | 26.2 | 41.5 |
| 15 | 20.5 | 0.0 | 4.7 | 74.8 |
| 16 | 23.0 | 15.7 | 19.0 | 42.3 |
| | 22.0 ± 7.9 | 4.1 ± 6.0 | 21.1 ± 9.5 | 52.8 ± 11.4 |

and the actual pathogenetic mechanisms of IgG4-related disease will also require further attention.

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ORIGINAL ARTICLE

# Clinical and histological changes associated with corticosteroid therapy in IgG4-related tubulointerstitial nephritis

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**Abstract**
*Objectives* This study aimed to investigate the clinicopathological changes induced by corticosteroid therapy in immunoglobulin (Ig)G4-related tubulointerstitial nephritis (TIN).
*Methods* We studied six IgG4-related TIN patients receiving renal biopsies before and after corticosteroid therapy. Their clinical data and histological findings were evaluated before and after therapy.
*Results* Elevated serum creatinine levels rapidly improved after corticosteroid therapy except for two patients, in whom it persisted. Abnormal radiological findings improved in all patients, although focal cortical atrophy persisted in three. Histologically, TIN-like dense lymphoplasmacytic infiltration, interstitial fibrosis, IgG4-positive plasma cell, CD4+CD25+ T cell, and Foxp3+ cell infiltration were characteristic before therapy. After therapy, the area with cell infiltration decreased and regional fibrosis became evident in the renal interstitium. The number of IgG4-positive plasma cells and Foxp3+ cells significantly diminished even in the early stage of therapy, whereas low to moderate numbers of CD4+ and CD8+ T cells still infiltrated where inflammation persisted in the later stage.
*Conclusions* Our study shows that persistent renal insufficiency associated with macroscopic atrophy and microscopic fibrosis is not so rare in IgG4-related TIN. Pathologically, the behavior of regulatory T cells during the clinical course is quite similar to that of IgG4-positive plasma cells, and the behavior pattern of those cells is distinctive.

**Keywords** IgG4-related disease · Tubulointerstitial nephritis · IgG4-positive plasma cell · Regulatory T cell · Corticosteroid therapy

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## Introduction

Immunoglobulin (Ig)G4-related disease (IgG4-RD) is a recently recognized systemic inflammatory disease with multiorgan involvement [1–5], including the kidney. Since 2004, accumulated case reports and case series have defined the radiographic and histopathological characteristic findings of IgG4-related kidney disease [6–20]. Two large